The Isolation and Synthesis of Neodolastane Diterpenoids

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REVIEW

The Isolation and Synthesis of Neodolastane Diterpenoids†

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The neodolastane diterpenoids comprise a group of 44 compounds including guanacastepenes, heptemerones, plicatilisins, radianspenes, 2,15-epoxy-5,13-dihydroxyneodolast-3-en-14-one and sphaerostanol. These fungal and marine natural products are characterized by tricyclic neodolastane skeleton which consists of fused five-, seven- and six-membered rings. The reported antibiotic activity against antibiotic-resistant bacteria together with strong antifungal and anticancer activities and their novel structures render these compounds as interesting synthetic targets. The aim of this account is to summarise the progress in the isolation, characterisation and synthesis of these diterpenoids as well as to review their biogenetic origin and diverse biological activities since their discovery in 2000.

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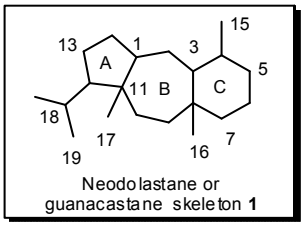
1 Introduction

Natural products have served as a rich source of biologically active substances and as a precious wealth in drug discovery processes.[1-4] Approximately 50% of the small pharmaceutically important molecules during the period from 2000 to 2010 have been connected to the field of natural products.[5] Since their early history and Ružička's discovery of "Biogenetic Isoprene Rule" in 1953,[6] terpenoids[7] have emerged as the largest family among natural molecules, with about 360 diverse and complex skeletal types and over 55,000 members.[8] In the past, most of these compounds have been isolated from plants, whereas in recent years, novel skeletons have emerged mostly from fungal[9] and marine resources.[10-13]

Due to their unique structures and interesting biological activities, tricyclic C_5-C_7-C_6 diterpenoids[14] represent excellent targets for total synthesis.[15] In particular, neodolastanes, a structurally diverse family of 44 diterpenoids which includes guanacastepenes, heptemerones, plicatilisins, radianspenes, 2,15-epoxy-5,13-dihydroxyneodolast-3-en-14-one and sphaerostanol,[16, 17] inspired numerous synthetic research groups. The studies towards their syntheses were the subject of Mischne's (2005),[18] Hierseman's (2005 & 2006),[15, 19] and Lee's (2006),[20] reviews. The excellent review by Baran (2007) on modern synthesis of biologically active terpenoids also shortly address the synthesis of guanacastepenes.[21]



Neodolastane or guanacastane skeleton **1**

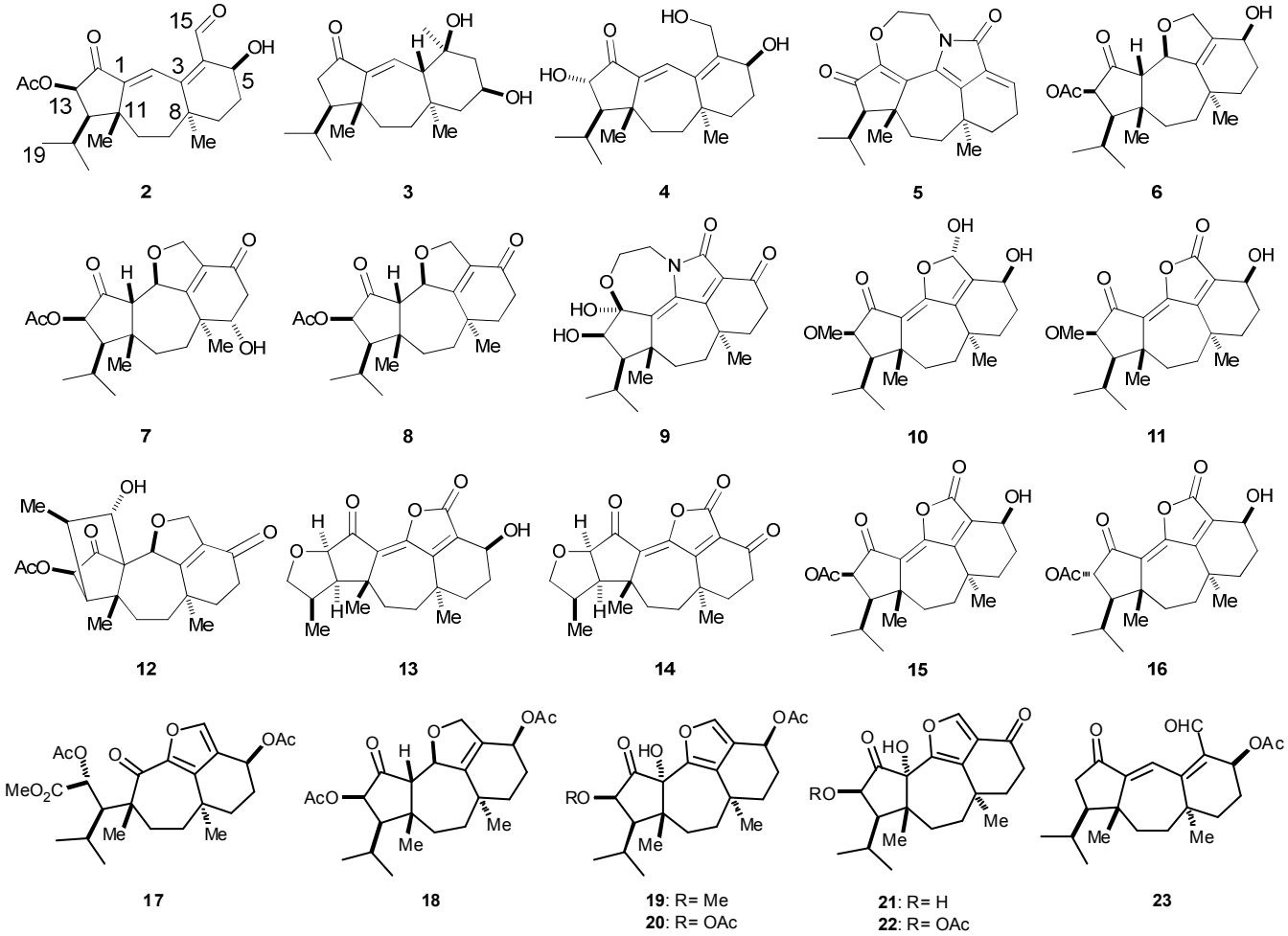
Neodolastane skeleton **1** was firstly proposed by Vidari as an intermediate in the biosynthesis of trichoaurantianolide A in 1995.[22, 23] Due to the geographical origin of the first characterised member of the family, guanacastepene A (**2**) found in Guanacaste region of Costa Rica, Clardy and co-workers rename the skeleton to guanacastane skeleton **1** (2000).[16] Similarly to **2**, guanacastepenes B-O (**3**-**16**) were

isolated a year later form endophytic fungus CR115 growing on the branches of *Daphnopsis americana* (Thymelaeaceae) tree.[17] Isoskeletal heptemerones A-G (**17-23**) were extracted from a fungus, *Coprinus heptemerus* (Psathyrellaceae) (2005),[24] and 2,15-epoxy-5,13-dihydroxyneodolast-3-en-14-one (**24**) from basidiomycetes of *Trametes corrugata* (Polyporaceae) (2009).[25] Sphaerostanol (**45**) was obtained from the red algae (Sphaerococcaceae) (2010),[26] radianspenes A-M (**25-36**) from fungal strains *Coprinus radians M65* (Coprinaceae) (2012),[27] and plicatilisins A-H (**25-36**) from basidiomycete of macro-fungi, *Coprinus plicatilis 82* (Coprinaceae) (2014).[28, 29]

In the context of this review, we summarise the advances in the isolation and characterisation of diterpenoids with neodolastane skeleton **1**. The diversity of structural motifs in connection to the detailed conformational analysis of the guanacastepene A are disclosed as well as biogenetic pathway and the biological activities. Lastly, synthetic studies and achievements in the total synthesis of guanacastepenes and heptemerones published after 2006 are discussed. The work reported earlier was summarized in previous reviews[15, 18-21] and is briefly reported here (*vide supra*).

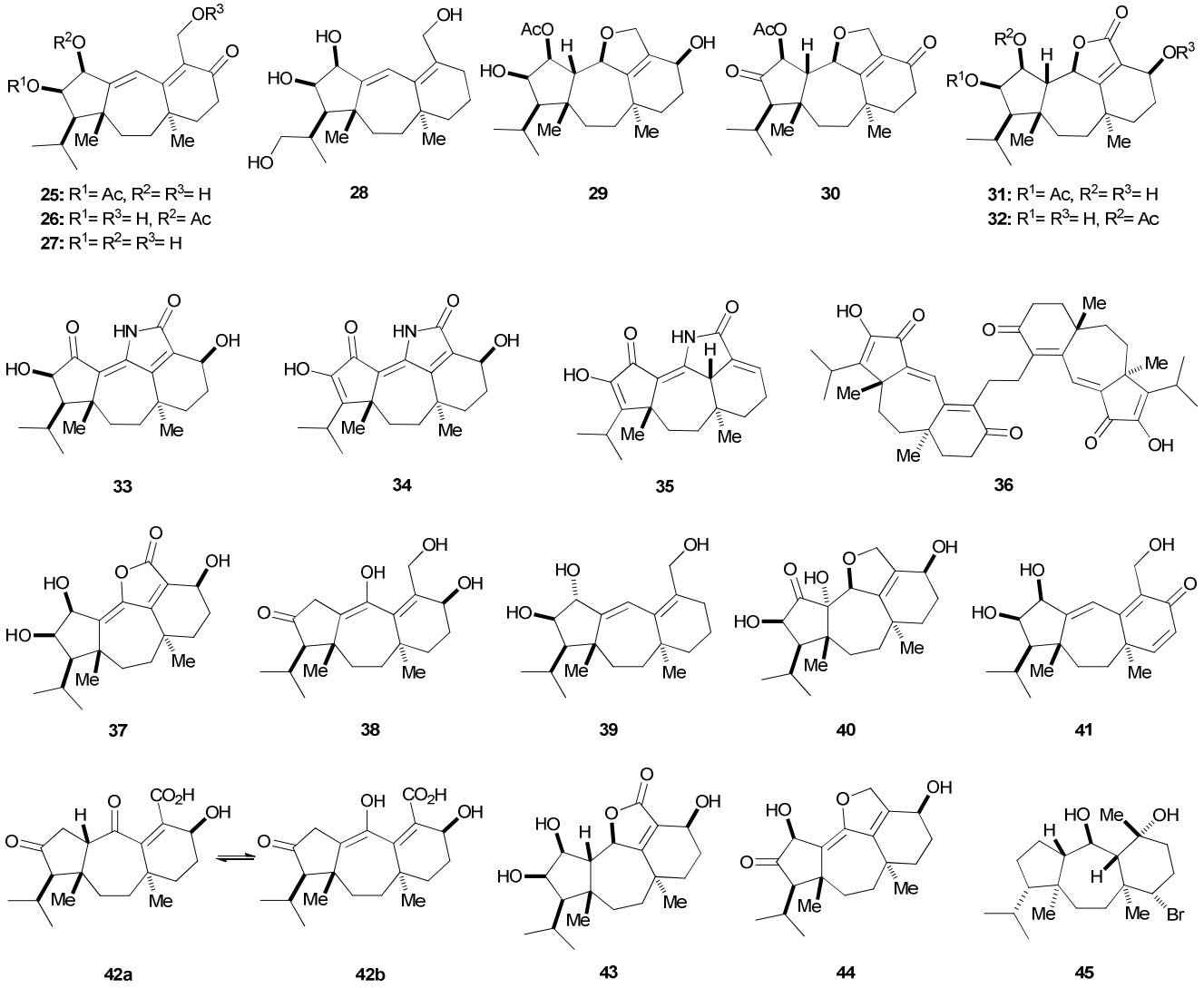
2 Structural diversity of neodolastanes

The structures of guanacastepenes A–O (**2-16**) were determined by X-ray crystallography.[16, 17] The family is characterized by the typical tricyclic C_5-C_7-C_6 neodolastane skeleton **1**. Many members have supplementary heterocyclic and carbocyclic rings. Fused furan or pyrrole systems whose heteroatom is positioned at C2, are present in guanacastepenes D-O, (**5-16**). 1,4-Oxazepine motif exists in guanacastepenes D (**5**) and H (**9**). Guanacastepenes L (**13**) and M (**14**) possess an additional fused tetrahydrofuran arriving from cyclisation at C13 while guanacastepene K (**12**) contains the more complex norbornane ring system.



In 2005, Sterner and co-workers isolated and characterised seven new neodolastanes, named heptemerones A-G, (**17-23**).[24] The heptemerone family was presented with the same C8- and C11-configurations as reported for the guanacastepenes although only the relative configurations were determined (the same numbering as for neodolastane skeleton (**1**)). The final

proof of the absolute configuration was obtained by the first total synthesis of (-)-heptemerone B (**18**) conducted by Trauner's group,[30] presuming that other members of the family have the same absolute configuration. Indeed, configuration and substitution patterns of heptemerones are similar to guanacastepenes. For example, the structure of heptemerone G (**23**) resembles the structure of guanacastepene A (**2**), but is missing an acetoxy group at C13. Other members of this family possess an additional furane ring connecting C2-C3-C4 and C15 atoms similarly to guanacastepenes E-G, (**6**-**8**). A supplementary hydroxyl group at C1 can be found for heptemerones C-F, (**19**-**22**) and interestingly, the A ring of heptemerone A (**17**) is oxidatively cleaved.



In 2009, Liu and co-workers reported the isolation of a new diterpenoid named 2,15-epoxy-5,13-dihydroxyneodolast-3-en-14-one (**24**) together with guanacastepene E (**6**).[25] The similar spectroscopic data of **24** to those of **6** and **18** indicated that compound **24** is their 5-*O*-and 13-*O*-deacetylated version.

Shen *et al.* (2012) isolated thirteen diterpenoids named radianspenes A-M, (**25**-**36**).[27] Their structures were compared to the guanacastepenes. Radianspene A (**25**), B (**26**) and C (**27**) resemble guanacastepene A (**2**) structure, whereas radianspenes E-I, (**29**-**32**) are related to guanacastepene E (**6**), with *O*-atoms at the same positions, but at different oxidation stages. Interestingly, the additional oxidation at C-19/C-20 in the terminal position of the isopropyl group is present in the radianspene D (**28**). Thus, this compound can be considered as the "missing link" in the biogenesis of guanacastepenes K-M, (**12**–**14**) (*vide infra*).

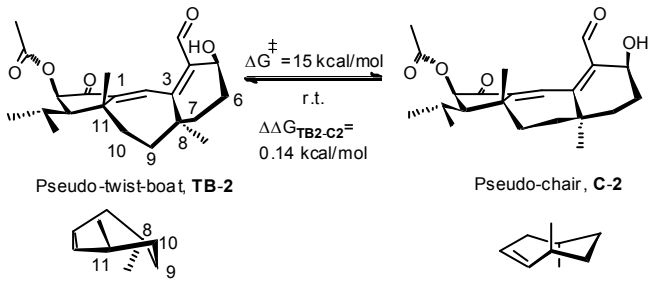
More recently, the same group isolated eight new neodolastanes named plicatilisins A-H (**37**-**44**) from fungi *Coprinus plicatilis*.[28, 29] The relative configuration of plicatilisin A (**37**) was suggested from NOESY experiments and compared to published data for guanacastepene N (**15**). The lactone ring of plicatilisin B (**38**) is opened and reduced to diol, whereas C14 and C13, which bear hydroxyl moieties in plicatilisin A (**37**), are replaced by methylene and ketone groups, respectively. Interestingly, plicatilisin C (**39**) is the only member of guanacastepenes-like diterpenoids with an *anti*-relation between the two hydroxyl groups at C13- and C14-atoms. Compared to other members of the family, plicatilisin D (**40**), G

(**43**) and H (**44**) have a supplementary furan-derived ring, similar to guanacastepenes E (**6**), F(**7**), J (**11**) or N (**15**). Plicatilisin E (**41**) is structurally related to radianspene C (**27**), with an additional double bond between C6-C7. Plicatilisin F (**42**) undergoes the keto-enol tautomerisation and can be correlated to guanacastepene A (**2**).

The structure of a new bromoditerpenoid alcohol, sphaerostanol (**45**), and its relative stereochemistry, was elucidated by Roussis and co-workers.[26] Oppositely from molecules of terrestrial origin, this marine natural product **45** is fully saturated and possesses the angular methyl groups in a *cis*-relationship with the halogen atom located at C7.

3 Conformational analysis of guanacastepene A structure

Pseudo-twist-boat **TB-2** and pseudo-chair **C-2** conformations of guanacastepene A with their corresponding energies as computed by the MM2 force field calculations are shown in Scheme 1. In the pseudo-twist-boat conformation **TB-2** the molecule is bent. This conformation was observed in the X-ray crystal structure and surprisingly, it is 0.14 kcal/mol less stable than the corresponding pseudo-chair conformation **C-2** with an energy barrier of 15 kcal/mol at r.t., as computed by Clardy *et al.*[16] Although there has been some disagreement in the literature, in the case of non-substituted cycloheptene, the calculations of several groups indicate the preference of the chair over the twist conformation by 0.57-1.10 kcal/mol.[31] The observed conformational isomerism can explain the missing ^{13}C-NMR signals as the isomers can slowly interconvert at r.t. and populate both conformational states, thus masking many of the NMR signals at the NMR time scale. The cycloheptene ring is fused to cyclohexene *via* sp^2 C3- and all carbon quaternary C8-atoms. The cyclohexene ring is in a half-chair conformation with the hydroxyl group in pseudo-axial position. Interestingly, alkene orbitals of α,β-unsaturated aldehyde and α,β-unsaturated ketone are almost perpendicular to each other, greatly diminishing electron exchange and, thus, these groups can be considered as two distinct entities in a pseudo-twist-boat conformation **TB-2**. However, the rotation around C5-C6 and C6-C7 bonds allows the inter-conversion from one to another half-chair that permits better overlap of orbitals in the 1,3-dienyl system.



Scheme 1. The equilibrium between pseudo-twist-boat **TB-2** and pseudo-chair **C-2** conformations of guanacastepene A (**2**) and their corresponding free energies as computed by Clardy and co-workers using MM2 force field calculations at r.t. and as confirmed by X-ray analysis.

4 Biogenesis of guanacastepenes

Neodolastane skeleton **1**[22] is related to marine origin dolastane skeleton[32, 33] by the transannular cyclisation or to the neodolabellanes by a Wagner Meerwein migration of methyl group from the dolabellane skeleton **46** (Fig. 1).[34-37] Although no biosynthetic studies on this family of compounds were conducted, Clardy[16, 17] and Hiersemann[15] proposed biogenesis of neodolastane skeleton as a series of enzyme-catalysed ring closures and Wagner Meerwein migrations from geranylgeranyl pyrophosphate (**47**) (Schemes 2 and 3).

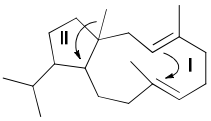


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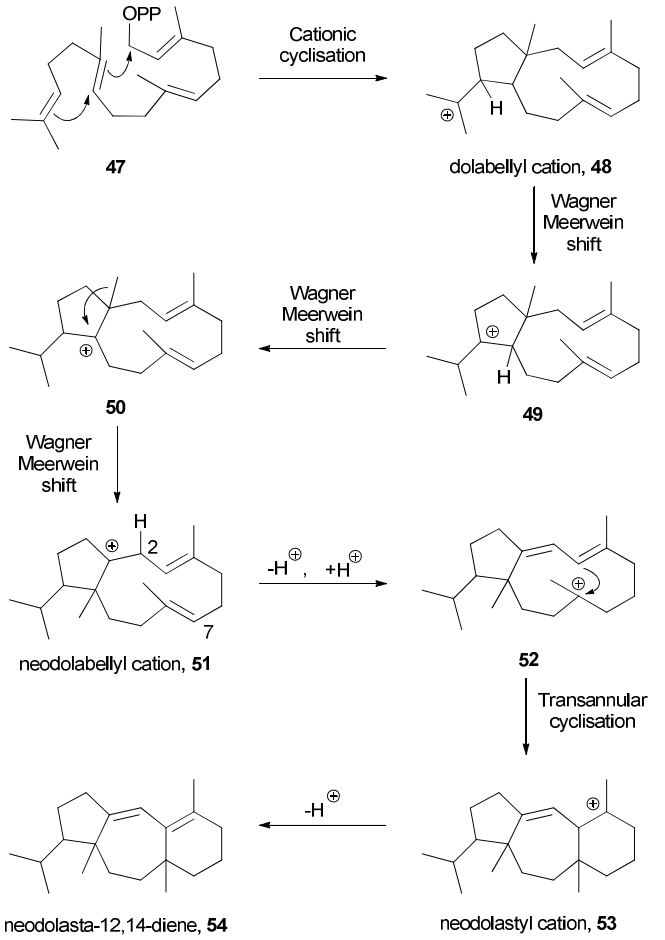
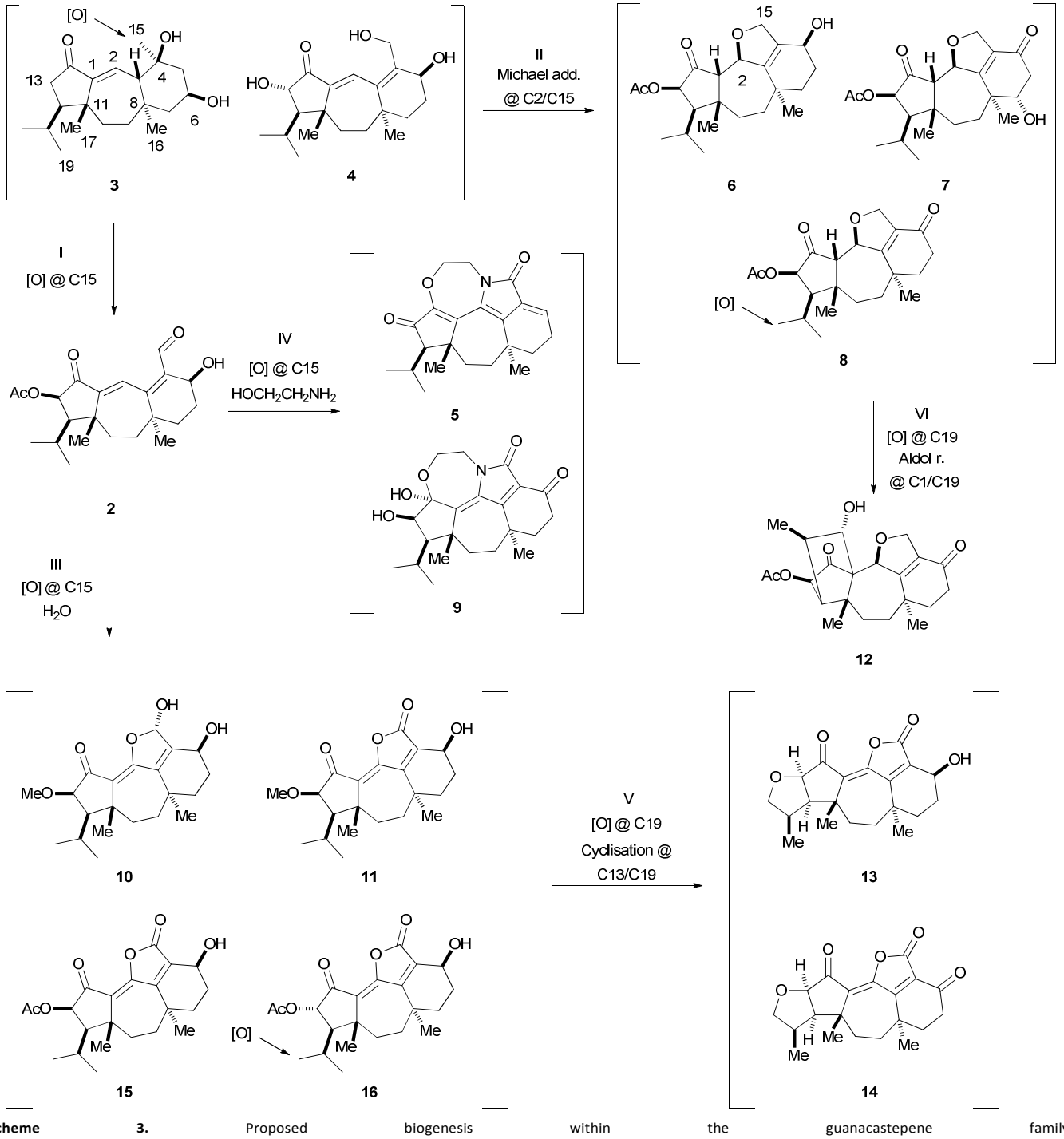
Fig. 1 The dolabellane skeleton (**46**) is a precursor of dolastane, neodolabellane and neodolastane skeletons by biosynthetic pathways I, II and I+II, respectively. Dolastane skeleton is formed by the transannular cyclisation (transformation I). Neodolabellane skeleton is obtained by the Wagner Meerwein migration of methyl group from C1 to C11 (transformation II) and guanacastane by the Wagner Meerwein migration and the transannular cyclisation (transformations I+II).



Scheme 2. Proposed biogenesis of the neodolastane skeleton **1**.

Two sequential cyclisations of **47** with the loss of the pyrophosphate group led to the formation of dolabellyl carbocation **48**, which undergoes [1,2]-rearrangements of hydrides and affords the carbenium ion **50**. Subsequent Wagner Meerwein migration of the methyl group gives the neodolabelly cation **51**. The elimination of proton at C2 and reprotonation at C7 produces carbocation **52** that is a substrate for a transannular cyclisation to give neodolastyl carbocation **53**. The latter eliminates the proton at C4 and forms an unsaturated version of neodolastane skeleton **1,** neodolasta-12,14-diene, (**54**).



Scheme 3. Proposed biogenesis within the guanacastepene family.

Scheme 3 shows possible further modification of the skeleton within the guanacastepene family. The proposed biogenesis includes transformations I-VI.[17] The simplest members are guanacastepenes B (**3**) and C (**4**) and their oxidised counterpart

guanacastepene A (**2**), (transformation I). The functionalisation and oxidation of these compounds or compounds similar to them leads to the formation of more complex skeletal systems of gunacastepenes D-O, (**5-16**). For instance, guanacastepenes E-G, (**6-8**) are the products of direct Michael addition of C15-OH to the α,β-unsaturated ketone. Guanacastepenes I (**10**), J (**11**), N (**15**) and O (**16**) or guanacastepenes H (**9**) and D (**5**) can be produced by the oxidation of the C15-angular group followed by intermolecular Michael addition of water (transformation III) or ethanolamine (transformation IV), respectively. Oxidation of the isopropyl methyl group into an alcohol followed by intramolecular cyclisation provides skeleton typical for guanacastepenes L (**13**) and M (**14**) (transformation V) whereas guanacastepene K (**12**) can be formed by the aldol reaction of aldehyde at C19/C20 with enolate at C1 (transformation VI). Tautomeric and conformational equilibria may still lead to a greater structural diversity.

5 Biological activities

The action of neodolastanes on living organisms are diverse. These natural products have essentially been the object of preliminary biological studies while the comprehensive biological assays or studies concerning structure-activity relationships were not conducted. As depicted in Tables 1-3, these diterpenoids were tested as antibiotic, antifungal and anticancer agents. Importantly, guanacastepene A (**2**) showed antibiotic activity against antibiotic-resistant Gram-positive bacteria (Table 1a).[16, 17, 38] This compound also exhibited moderate activity against a panel of Gram-positive and Gram-negative bacteria as well as *Candida albicans*. Although the antibacterial activities of heptemerones were weak (Table 1b) this family of compounds showed potent activity against the fungal germination (Table 2).[39] Cytotoxicities of these compounds were moderate (Table 3a) and apart from heptomerone D (**20**), other members of the family were not phytotoxic. *In vitro* IC_{50} growth inhibitory values of radianspenes,[27] plicatilisins[28, 29] and phaerostanol (**45**)[26] against different tumour cell lines were also determined (Table 3b-d). Among them, the most important is the cytotoxic activity of radianspene C (**27**) with an IC_{50} value of 0.91 μM against breast adenocarcinoma.

In further text, the results of antibiotic, antifungal and cytotoxic tests concerning the mentioned diterpenoids are systematically summarised.

5.1 Antibiotic activities

The screening of biological activities of guanacastepene A (**2**) revealed antibacterial properties against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VREF) (Table 1a).[16, 38] When agar plates streaked with MRSA were treated with 50 μg of guanacastepene A (**2**) or 30 μg of vancomycin, 7-10 mm and 17 mm zones of growth inhibition were observed, respectively. The same treatment against VREF produced 8 mm antibacterial inhibition zones for guanacastepene A (**2**) while vancomycin was not active. Guanacastepene A also showed activity against *Escherichia coli* and *Candida albicans*. Nevertheless, further biological studies severely diminished the potential of guanacastepene A (**2**) to be employed as a potential antibiotic agent due to its moderate activity against bacteria and the haemolytic activity against human red blood cells, most likely by nonspecific membrane lysis.[38] To the best of our knowledge, biological assays of other members of the guanacastepene family, B-O (**3-16**), have never been reported.

a)	Compound;[a] c [μg/ml]		
	2; 50	Methicillin; 5	Vancomycin; 30
Gram (+)			
Staphylococcus aureus 375	7-10H[b]	15-22H[b]	15
Staphylococcus aureus 310	6-9H[b]	0	17
Enterococcus faecium 379	8H[b]		0
	2; 50	Nystatin; 100	Bleomycin; 100
Gram (-)			
Escherichia coli 389	8H[b]		
Escherichia coli 442	5H[b]		
Candida albicans 54	5-9H[b]	16-24H	
BIA[d]	9T[c]		3+[e]
b)		**19**, **20**, **23**	
Gram (+)			
Micrococcus luteus; *Corynebacterium insidiosum*; *Bacillus brevis*; *Bacillus subtilis*		Bacteriostatic at	
Gram (-)			
Pseudomonas fluorescens		20 μg/ml	

Table 1. a) Antibiotic activity of guanacastepene A (**2**). Reported values are zones of growth inhibition in millimetres. b) Bacteriostatic activities of heptomerones C (**19**), D (**20**) and G (**23**) towards different bacteria.

[a]5 ml of each concentration was spotted on the agar surface. Plate was incubated for 18h at 37°C. Zone of growth inhibition: [b]H, hazy; [c]T, toxic; [d]BIA (Biochemical Induction Assay): detects DNA damaging activity; [e]strong DNA damage.

Antibiotic activities of heptemerones were also examined by Anke and co-workers.[39] Heptemerones C (**19**), D (**20**) and G (**23**) were bacteriostatic against Gram-positive bacteria *Micrococcus luteus*; *Corynebacterium insidiosum*; *Bacillus brevis*; *Bacillus subtilis* and Gram-negative bacteria *Pseudomonas fluorescens.* at 20 μg/ml concentration (Table 1b). The zones of growth inhibition of heptemerone G (**23**), the most active compound of the family, was in the same range as guanacastepene A (**2**). The authors proposed that an α,β-unsaturated aldehyde and an α,β-unsaturated ketone are probably the active pharmacophores responsible for the antibiotic activities. When they reacted heptemerone G (**23**) with cysteine (1 equiv.), the antibacterial activities were negligible in an hour. These results are in agreement with the non-selective inhibition of all macromolecular syntheses in

Magnaporthe grisea or *E. coli* by heptemerone G (**23**)[39]and guanacastepene A (**2**),[38] respectively.

5.2 Antifungal activities

Anke and co-workers also examined the antifungal activities of heptemerones against *Bipolaris victoriae*, *Botrytis cinerea*, *Colletotrichum graminicola*, *Drechslera oryzae*, *Fusarium solani*, *Magnaporthe grisea*, *Ascochyta pisi*, *Cladosporium cladosporioides*, *Penicillium notatum* and *Septoria tritici* (Table 2a).[39] Heptemerone G (**23**) was the most active compound with minimum inhibitory concentration (MIC) in the range of 1μg/ml. Interestingly, MIC is highly influenced by the composition of the assay medium. In water heptemerones were 5-10 times more active than in complex YMG-media (0.4% glucose and Czapek yeast medium). Heptemerone G (**23**) also inhibited the growth of *M. grisea* at 1 μg/ml in the leaf segment assay with *Oryza sativa* and *Hordeum sativum* (Table 2b).

Table 2. a) Inhibition of germination of conidia by heptomerones C (**19**), D (**20**), F (**22**) and G (**23**). b) Antifungal activities of same compounds in the leaf segment assay with *Oryza sativa* and *Hordeum sativum. M. grisea* was used as plant-pathogenic fungus. Values given are MIC [μg/ml].

a)	C (**19**)	D (**20**)	F (**22**)	G (**23**)
Bipolaris victoriae (H_2O)	>100	>100	>100	20
Botrytis cinerea (H_2O)	20	20	50	5
Colletotrichum graminicola (H_2O)	10	20	50	1
Drechslera oryzae (H_2O)	20	20	20	10
Fusarium solani (H_2O)	>100	>100	>100	20
Magnaporthe grisea (H_2O)	10	20	20	1
Ascochyta pisi (YMG[a])	>100	>100	>100	10
Cladosporium cladosporioides (YMG[a])	>100	>100	>100	20
Penicillium notatum (YMG[a])	50	>100	>100	20
Septoria tritici (YMG[a])	>100	>100	>100	20
b)				
Oryza sativa	10	20	10	1
Hordeum sativum	20	50	50	1

[a]YMG-medium consists of glucose 1%, malt extract 1% and yeast extract 0.4% in tap water at 22°C.

5.3 Cytotoxic activities

The cytotoxic activities of heptomerones were examined *in vitro* against four human cancer cell lines including T cell leukaemia (Jurkat), monocytic leukaemia (Mono-Mac-6), cervical cancer (HeLa) and hepatocellular carcinoma (HepG2) (Table 3a).[39] Heptemerone G (**23**) was again the most active against Mono-Mac-6 with an IC_{50} value as low as 2.8 μM. Although no activities of heptemerone A (**17**) in the other tests were observed, this compound possessed a cytotoxic activity in a range of 10.8-216.3 μM. Heptemerones A (**17**) and C (**19**) also displayed an interesting cytotoxic activities.

The *in vitro* cytotoxicity of radianspenes[27] and plicatilisins[28, 29] were evaluated against human cancer cell lines using cisplatin or doxorubicin as positive controls (Table 3b and c). The tests were conducted using breast adenocarcinoma (MDA-MB), hepatocellular carcinoma (HepG2), cervical cancer (HeLa), stomach adenocarcinoma (BGC-823), colon cancer (HCT 116), and osteosarcoma (U2OS) cell lines. Acetate exchange for radianspenes A (**25**), B (**26**), E (**29**), H (**31**) and I (**32**) was observed under testing conditions. Notably, the radianspene C (**27**) exhibited significant cytotoxic activity with IC_{50} of 0.91 μM against the human breast carcinoma MDA-MB-435 cell line (Table 3b). Plicatilisin A (**37**) showed relevant cytotoxicity with IC_{50} values ranging from 1.2 to 6.0 μM against six human cancer cell lines (Table 3c). Plicatilisin B (**38**) and D (**40**) were also active at the IC_{50} concentrations as low as 17 μM (Table 3c).

The *in vitro* anti-tumour activity of sphaerostanol (**45**) was probed together with 15 other isolated secondary metabolites against four human apoptosis-resistant (U373, A549, SKMEL-28, OE21) and two human apoptosis-sensitive (PC-3, LoVo) cancer cell lines (Table 3d).[26] Although sphaerostanol (**45**) was not the most active compound of this series, it showed IC_{50} values in range from 64-94 μM with the mean IC_{50} *in vitro* growth inhibitory value of 76 μM.

a)

	IC_{50}/[μM][a]			
	Jurkat	Mono-Mac-6	HeLa S3	HepG2
17	10.8-21.6	43.3	216.3	>216.3
18	119.5	>239.0	>239.0	>239.0
19	12.4-24.7	24.7	49.4	49.4
20	46.3-115.7	23.1	231.4	231.4
21	144.3	144.3	288.6	144.3
22	25.7	51.5	257.4	257.4
23	5.6	2.8	55.7	55.7

b)

	MDA-MB-435
27	0.91

c)

	HepG2	HeLa	MDA-MB-231	BGC-823	HCT-116	U2OS
37	2.3	5.0	6.0	2.4	1.2	19.3
38	25.9	>50.0	>50.0	>50.0	38.9	>50.0
40	16.9	>50.0	34.8	35.6	19.8	39.7

d)

	U373	A549	OE21	SKMEL-28	PC-3	LoVo
45	85	97	60	96	74	64

Table 3. IC_{50} *in vitro* growth inhibitory values of: a) heptomerones A-G, **17-23**; b) radianspene C (**27**); c) plicatilisins A (**37**), B (**38**) and D (**40**); and d) 5(**45**) against different tumour cell lines.

[a]human cancer cell lines, which include T cell leukaemia (Jurkat), monocytic leukaemia (Mono-Mac-6), cervical cancer (HeLa), hepatocellular carcinoma (HepG2), breast adenocarcinoma (MDA-MB), stomach adenocarcinoma (BGC-823), colon cancer (HCT 116), osteosarcoma (U2OS), glioblastoma (U373), non-small-cell-lung cancer (A549), oesophageal cancer (OE21), melanoma (SKMEL-28), prostate cancer (PC-3) and colon cancer (LoVo).

6 Synthetic approaches

A wide range of original synthetic approaches to guanacastepene and heptemerone tricyclic skeletons have been developed and can be broadly divided into three groups: a) synthesis of hydroazulene core, b) synthesis of tricyclic guanacastepene scaffolds and c) total synthesis of

guanacastepenes and heptomerones. Thus, the results of the syntheses are accordingly summarised in further text.

6.1 Synthesis of hydroazulene core

Disconnection of C3-C4 and C7-C8 bonds has proven to be the most popular approach to the neodolastane skeleton **1** leading to hydroazulene core **55** (Fig. 2). The bicycle **55** was successfully synthesised by Magnus,[40, 41] Tius,[42] Chiu,[43] Srikrishna[44] and Greaney[45], while the approach *via* this synthon was also used in the total synthesis of guanacastepenes A, C and heptemerone G by Danishefsky,[52-61] Snider,[62-64] Mehta[73-76] and Wicha.[69-72]

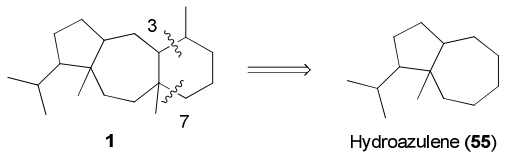
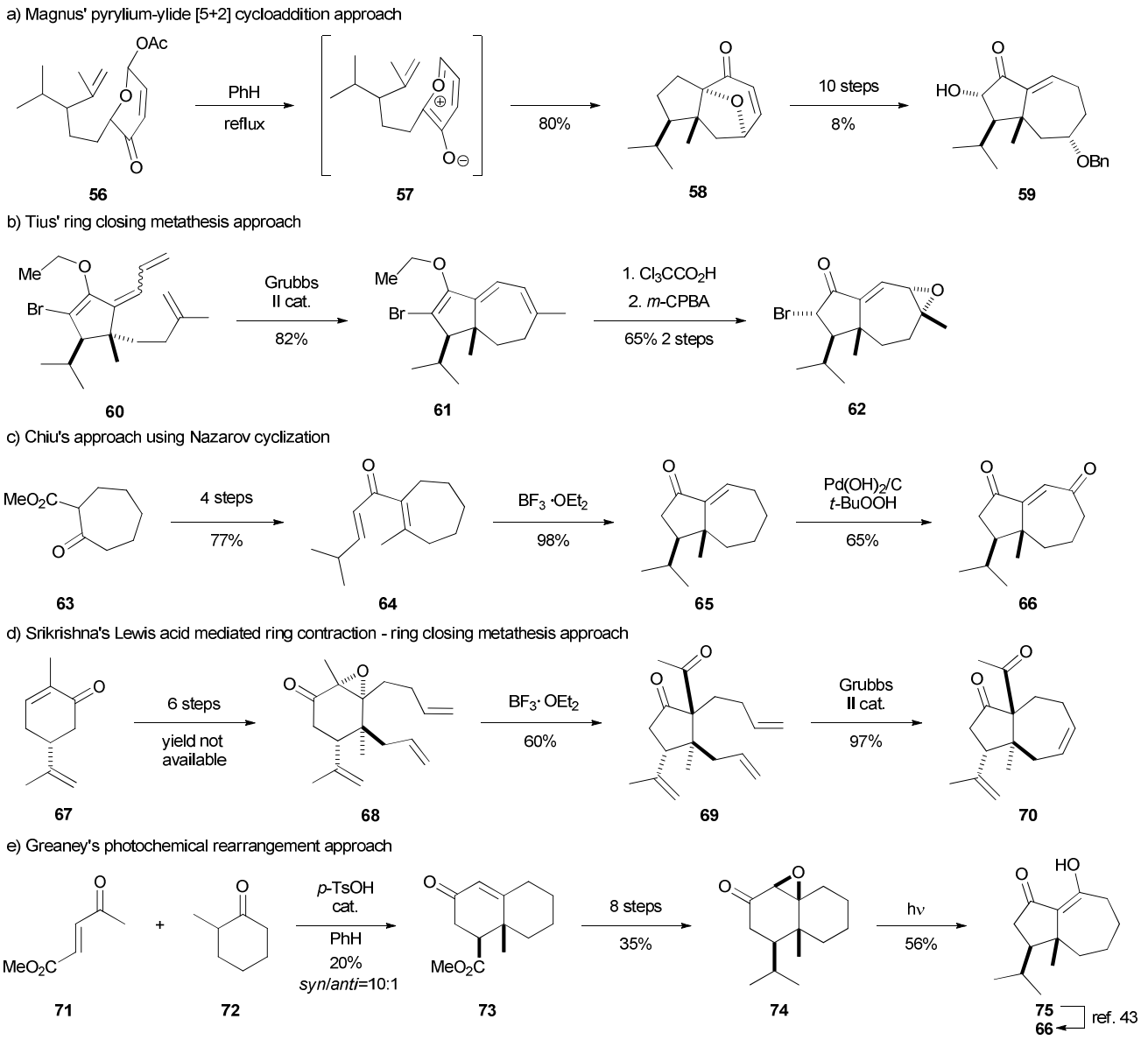


Fig. 2 The disconnection of guanacastane **1** to hydroazulene core **55**.

Table 4 and Scheme 4 summarise methodologies, key disconnections, number of steps and yields relevant to the construction of hydroazulene core **55**. Magnus' synthesis of synthon **55** relays on the C1-C11 and C9-C10 bond disconnections and was accomplished in 18 steps from commercially available isobutylmethyl ketone as shown in Table 4.[40, 41] The key step of the synthesis, a pyrylium-ylide [5+2] intramolecular cycloaddition, is highlighted in Scheme 4a. Elimination of acetic acid from the acetal **56** provided zwitterionic pyrylium-ylide **57** that smoothly underwent the stereoselective cycloaddition giving enone **58** in 80% yield.



Scheme 4. Realised approaches to 5-7 hydroazulene core **55**. *m*-CPBA= *meta*-chloroperoxybenzoic acid; *p*-TsOH= *para*-toluenesulfonic acid.

Table 4. The disconnection of guanacastane **1** to hydroazulene core **55** and overview of the used methodologies.

Entry	Group	Year	Methodology	Key Disconn.	Number of steps	Total yield/%	References
1.	Magnus	2001	pyrylium ylide [5+2] cycloaddition	C1-C11, C9-C10	18	1.9	34, 35
2.	Tius	2002	RCM	C3-C8	12	7.1	42
3.	Chiu	2004	Nazarov cyclisation	C11-C12	6	49.0	43
4.	Srikrishna	2004	RCM	C8-C9	9[a]	-[b]	44
5.	Greaney	2007	photochemical rearrangement	C1-C11	13	1.7	45

[a]asymmetric; [b]yield not available

This compound was further transformed into fully functionalised enone **59**. Tius'[42] and Srikrishna's groups[44] employed the ring closing metathesis approach to close the seven-membered ring disconnecting C3-C8 or C8-C9 bonds, respectively (Entries 2 and 4; Table 4; Scheme 4b and d). Metathesis of **60** under high dilution with second generation Grubbs catalyst afforded **61** (82%), which was further converted into epoxy ketone **62** in 65% yield. Chiu and co-workers reported an elegant synthesis of hydroazulene core **66** using a diastereoselective Nazarov cyclisation (Scheme 4c).[43] Ketoester **63** was first converted into dienone **64** in 4 steps with 77% yield. Lewis acid mediated Nazarov cyclisation of **64** provided hydroazulene core **65** (98%) as a single diastereomer in 98% yield. Thus, hydroazulene core **66** was obtained readily

in 6 steps with 49% overall yield from **63** (Entry 3; Table 4). Srikrishna's group utilised (*R*)-carvone (**67**) as a readily available chiral pool building block to install the stereochemistry of quaternary C11-stereocentre of hydroazulene core **70** (Scheme 4d). (*R*)-Carvone (**67**) was elaborated to α,β-epoxy ketone **68** in six steps. This compound underwent Lewis acid-mediated ring contraction to give triene **69**, which was then submitted to the RCM protocol to yield diketone **70** in 97%.

In 2007, Greaney and co-workers published the synthesis of Chiu's intermediate **66** (Scheme 4e).[45] Employing Robinson annulation, they formed enone **73** in 20% yield as a major diastereoisomer. The authors proposed that the yield is modest because of steric hindrance, which provokes very slow initial Michael addition. However, the thermodynamically favoured epimer with the ester group in the pseudo-equatorial position of cyclohexenone **73** was formed in a ratio *syn*-**73**/*anti*-**73** = 10:1. Hydrozulene core **71** was obtained by a photochemical rearrangement of keto-epoxide **74** in 56% yield and it was further transformed to Chiu's endione **66** in three additional steps *via* enone **65** (See also Scheme 4c).

6.2 Synthesis of tricyclic core of guanacastepenes

Table 5 summarises the synthetic approaches to guanacastepene core. In 2002, Lee utilised reductive ring closure as the key step to form C2-C3 bond.[20, 46, 47] Kwon (2003) employed Mukaiyama aldol reaction to construct C1-C2 bond[48, 49] and Brummond (2003) used Pauson-Khand reaction for the formation of C1-C11, C12-C13 and C13-C14 bonds.[50] Finally, Sato (2010) used his rhodium-catalysed hydroacylation cycloisomerisation methodology. The synthesis were achieved in eleven to nineteen steps with 2 to 34% overall yield.[51]

One of the first asymmetric synthesis of guanacastepene tricycle was reported by Lee and co-workers (Scheme 5a).[20, 46, 47] They synthesised intermediate **78** by copper-catalysed 1,4-addition of (1*S*)-citronellyl-derived Grignard reagent **77** to (1*S*)-verbenone **76**. Both reactants are readily available chiral pool materials. The formation of C2-C3 bond was performed by intramolecular SmI_2 reductive coupling of the aldehyde function of **79** onto the α,β-unsaturated ketone that provided guanacastepene I precursor **80** in 90% yield. This methodology also allowed the correct installation of stereochemistry at C8-quaternary carbon because thermodynamically more favoured cyclisation leading to *trans*-relationship of the two quaternary methyl groups.

Table 5. Different synthetic approaches to guanacastepene core.

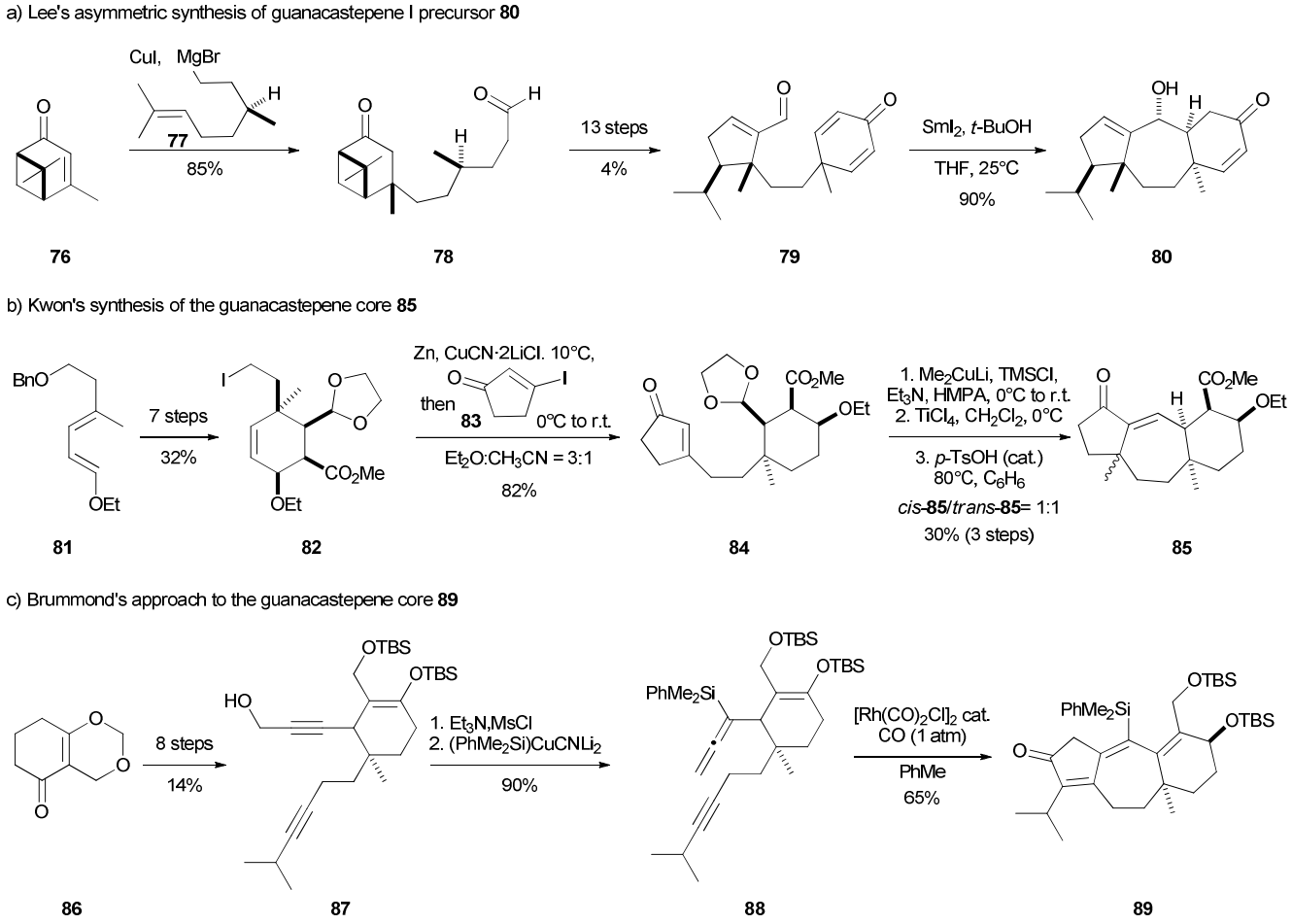
Entry	Group	Year	Methodology	Key Disconn.	Number of steps	Total yield (%)	References
1.	Lee[a]	2002	Reductive ring closure	C2-C3	19	2.1	20, 46, 47
2.	Kwon	2003	Mukaiyama aldol	C1-C2	13	6.0	48, 49
3.	Brummond	2003	Pauson-Khand reaction	C1-C11, C12-C13, C13-C14	11	8.2	50
4.	Sato	2010	Rh-cat. hydroacylation cycloisomerization	C1-C2, C11-C12	11	33.8	51

[a]asymmetric

In another study, Kwon and co-workers utilised a Diels–Alder reaction involving diene **81** which can be prepared from ethoxyacetylene in two steps with 74% yield, and maleic acid under high pressure and temperature to obtain the precursor of highly functionalised intermediate **82** (32%), as shown in Scheme 5b.[48, 49] Copper-catalysed conjugate addition of organozinc reagent of **82** to α,β-unsaturated ketone **83** gave **84** in an 82% yield. Sequential conjugate addition of Me_2CuLi to enone **84** and $TiCl_4$-mediated intramolecular Mukaiyama type aldol reaction was followed by the elimination catalysed by *p*-toluenesulfonic acid (*p*-TsOH) and produced two tricyclic epimers with methyl groups in *cis*- and *trans*-relationships, *cis*-**85** and *trans*-**85** (*cis*-**85**/*trans*-**85**=1:1, 30% for 2 steps). The methyl magnesium bromide addition catalysed by copper bromide dimethyl sulfide complex followed by elimination with *p*-TsOH improved the ratio to 1.2:1. By this synthetic route, guanacastepene core **85** was obtained in 13 steps with 6% overall yield (Entry 2; Table 5).

Brummond's group reported the construction of tricycle **89** by employing a rhodium-catalysed Pauson–Khand reaction (Scheme 5c).[50] Smith's enone **86** was transformed into dialkyne **87** in 14% over 8 steps. Mesylation of the pendant propargylic alcohol of **87** followed by the direct addition of $(Me_2PhSi)_2CuCNLi_2$ afforded the desired allene **88** in 90% yield over two steps. Rhodium-catalysed Pauson–Khand reaction successively formed C1-C11, C12-C13 and C13-C14 bonds of the hydroazulene system of skeleton **89** in 65% of yield. Due to steric hindrance of the isopropyl group, all further attempts to install the quaternary C11-stereocentre by copper-catalysed conjugate addition were not successful and led to fulvene containing product resulting from the dehydration of the 1,2-adduct. The overall yield of this reaction sequence was 8.2% for eleven steps (Entry 3; Table 5).

In 2010, Sato and co-workers reported a rhodium(I)-catalysed cascade reaction consisting of the hydroacylation cycloisomerisation steps leading to the easy formation of skeleton **93**.[51] The synthesis of the substrate *syn*-**91** was performed in a stereoselective manner from hemiacetal *syn*-**90** (Scheme 6). When *syn*-**91** was treated with a catalytic amount of $[Rh(dppe)]ClO_4$ (dppe = 1,2-bis(diphenylphosphino)ethane), generated *in situ*, the desired C_5-C_7-C_6 tricyclic compound *syn*-**93** (54%) and bicyclic *syn*-**94** (12%) were obtained *via* the intermediacy of eight-membered rhodacycle **92**. This procedure allowed the formation of three carbon-carbon bonds in one step and yielded *syn*-**93** in 34% overall yield over eleven steps (Entry 4, Table 5). Similarly, the treatment of *anti*-**91** produced the mixture of desired *anti*-**93** in 9% yield with contaminant formation of bicyclic *anti*-**94** (32%).



Scheme 5. Lee's, Kwon's and Brummond's approaches to guanacastepene-like cores **80**, **85** and **89**. HMPA = hexamethylphosphoramide.

6.3 Total synthesis of guanacastepenes and heptemerones

Table 6 summarises the methodologies, key disconnections, number of steps and yields of the conducted total syntheses of guanacastepenes and heptemerones. En route to guanacastepenes A (**2**) and C(**4**), Danishefsky,[52-61] Snider,[62-64] Mehta[73-76] and Wicha[70-72] formed the C3-C4 bond of the six-membered ring by Knoevenagel or intramolecular condensations while Hanna[65, 66, 84] used tandem ring closing metathesis reaction to build three new C-C bonds. Sorensen created the C10-C11 bond of central seven membered ring of guanacastepenes A (**2**) and E (**6**) by [2+2]-cycloaddition fragmentation methodology.[67,85] Yang's group used intramolecular Diels–Alder (IMDA) cycloaddition to construct the C3-C8 and C4-C5 bonds of the C8-*epi*-guanacastepene O, C8-*epi*-(**16**).[77] Overman employed the rare 7-*endo*-Heck cyclisation as a key step in his synthesis of guanacastepene N (**15**)[81] and Trauner developed electrochemical oxidation leading to formation of C1-C2 bond of heptomerone B (**18**) and guanacastepene E (**6**).[30] Finally, Carreira utilised his original methodology consisting of cycloinsertion and fragmentation steps to construct guanacastepene N (**15**) and guanacastepene O (**16**).[83] Statistically, 23 steps were needed to accomplish total synthesis of guanacastepenes or heptomerones with average yield of 2.7%.

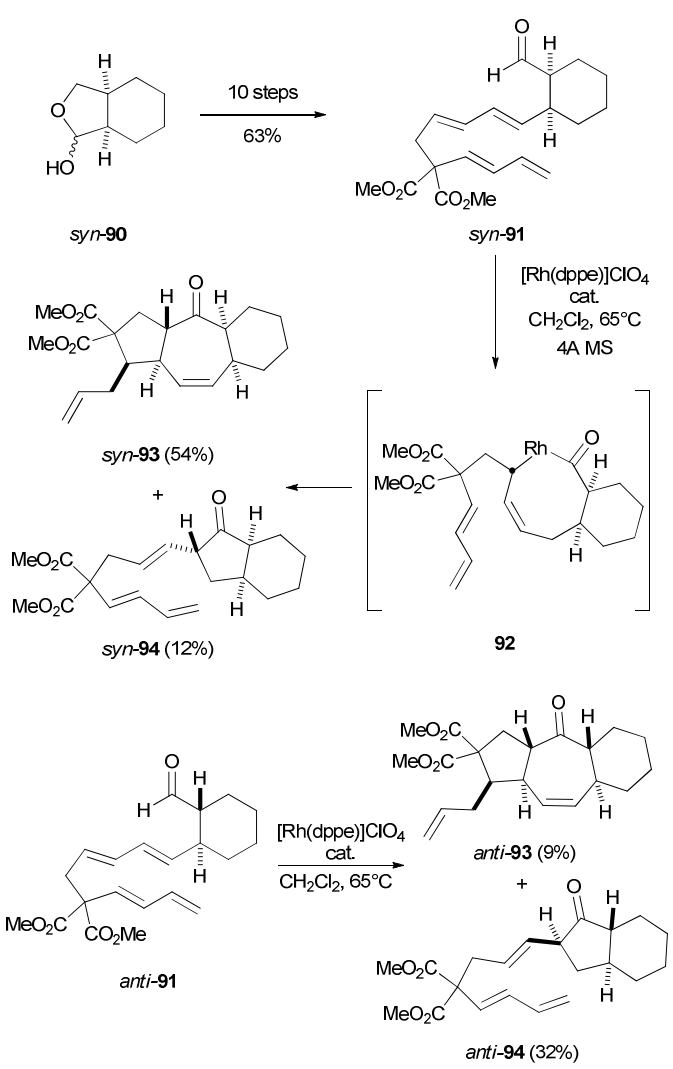
The pioneering work in total synthesis of guanacastepene A (**2**) was performed by Danishefsky's group.[54, 61] Many of the following synthetic studies developed reaction sequences to Danishefsky's intermediates or adopted his chemistry to solve the problematic synthetic steps. The synthesis of (±)-guanacastepene A (**2**) is outlined in Scheme 7. Ketone **96** was obtained in two steps with 71% overall yield from commercially available 2-methyl-2-cyclopentenone (**95**).[86] The intramolecular reductive cyclisation of vinyl iodide of **96** onto the pendant ketone was achieved *via* the vinyllithium intermediate generated *in situ* by halogen-metal exchange. The corresponding allylic alcohol underwent an oxidative rearrangement with PCC providing hydroazulene core **97** in 70% yield over 2 steps. From this intermediate, Danishefsky group developed different synthetic routs to correctly install the relative stereochemistry of C8 centre in *anti*–relationship respect to the angular methyl group at C11. Hydroazulene core **97** was finally transformed to β-ketoester **99** in 10 steps with 19% yield *via* intermediate **98**. The eliminative epoxide opening and intramolecular Knoevenagel condensation

furnished tricyclic intermediate **100** (74%) with completed neodolastane skeleton **1**. Further functionalisations were directed towards correct installation of the oxygenation and unsaturation groups at the north edge of the skeleton of guanacastepene core to provide acetonide **101** (50%) over four steps. Rubottom oxidation of silylenol ether derived from **101** with dimethyldioxirane followed by acetylation of the corresponding alcohol provided **102** with a correctly installed C13-acetoxy substituent.[58] Acetonide deprotection followed by rapid oxidation of an unstable diol completed the synthesis of (±)-guanacastepene A (**2**). Snider and co-workers utilised an intramolecular Prins type reaction and an aldol condensation as the key step in their formal synthesis of guanacastepene A (**2**) (Table 3 and Scheme 8).[62, 64] The synthetic intermediate **104** was obtained in 60% yield over 4 steps. The $EtAlCl_2$-promoted cyclisation followed by sequential [1,2]-hydride and methyl shifts of **104** provided the cyclopentanone **106** in 69% yield as the only cyclic product a with correct *syn*-stereochemistry of methyl and isopropyl groups. The latter in two steps was transformed into triene **107** (65%). The ring closing metathesis of **107** furnished a hydroazulene core **108** (88%) that was further elaborated to enone **109** (29%). Under basic conditions, the aldol condensation precursor **109** gave the desired tricyclic structure **110** that was transformed in 3 additional steps in Danishefsky's acetonide **101** with 42% overall yield.

Interesting formal total synthesis of guanacastepene A (**2**) based on Danishefsky's acetonide **101** using a tandem ring-closing-metathesis (RCM) was reported by Hanna and co-workers.[65, 66] As shown in Scheme 9, trienyne **112** was obtained from cyclopentanone **111** (9%) in 9 steps. This relatively simple substrate **112** underwent tandem ene-yne-ene RCM and rapidly built up tricyclic skeleton **113** (82%). Further functionalisation provided Danishefsky's acetonide **101** over seven steps.

Afterwards Hanna and co-workers prepared a series of tricyclic guanacastepene like structures **115a-e** (Table 7).[84] Authors probed the influence of substituents R^1 and R^2 on ring closing metathesis using second generation Grubbs catalyst. Except for **114c** that remained unchanged, all other dienynes were easily converted into the expected products in high yields (70-93%) regardless the R^1 and R^2 substitution.

Mehta's total synthesis of guanacastepene C (**4**) is disclosed in Scheme 10.[73-76] The authors used ring-closing-metathesis and Knoevenagel condensation as the key methodologies. Readily available *endo*-enone **116** was employed as a masked dienone to control the stereochemistry during the preparation of cyclopentanone **117** by exclusive reactivity on its *exo* face. Compound **116** was transformed into enone **117** in 6 steps with 27% overall yield. The ring closing metathesis of terminal alkenyl groups of **117** readily provided hydroazulene core **118** in 95% yield. β-Ketoester **119** was obtained in eighteen steps and underwent an intramolecular Knoevenagel condensation to provide the tricycle that was further transformed to guanacastepene C (**4**) in an eight step sequence.



Scheme 6. Sato's approach to the tricyclic cores **94**. dppe = 1,2-bis(diphenylphosphino)ethane.

In 2006, Sorensen's group reported an asymmetric formal synthesis of guanacastepene A (**2**) and a first total synthesis of guanacastepene E (**6**) (Schemes 11 and 12).[67] They employed (*S*)-(+)-carvone (**67**) as a chiral pool starting material to introduce C12-stereocentre of cyclopentanone portion **123** of the molecule as a single enantiomer in an 8 steps sequence with 11-14% yield. The α-acyloxy nitrile **121**, obtained in 5 steps (41%) from **67**, was deprotonated with lithium bis(trimethylsilyl)amide (LiHMDS) to afford the enol tautomer, dione **122** in 58% yield *via* the intermediacy of postulated epoxy alkoxide ion **121**. The exchange of vinyl nonafluorobutanesulfonate (Nf) from **122** to vinylstannane **123** by palladium-catalysed coupling with hexamethylditin was challenging due to the steric effect of isopropyl group and leads to the formation of **123** in 59% yield over 2 steps.

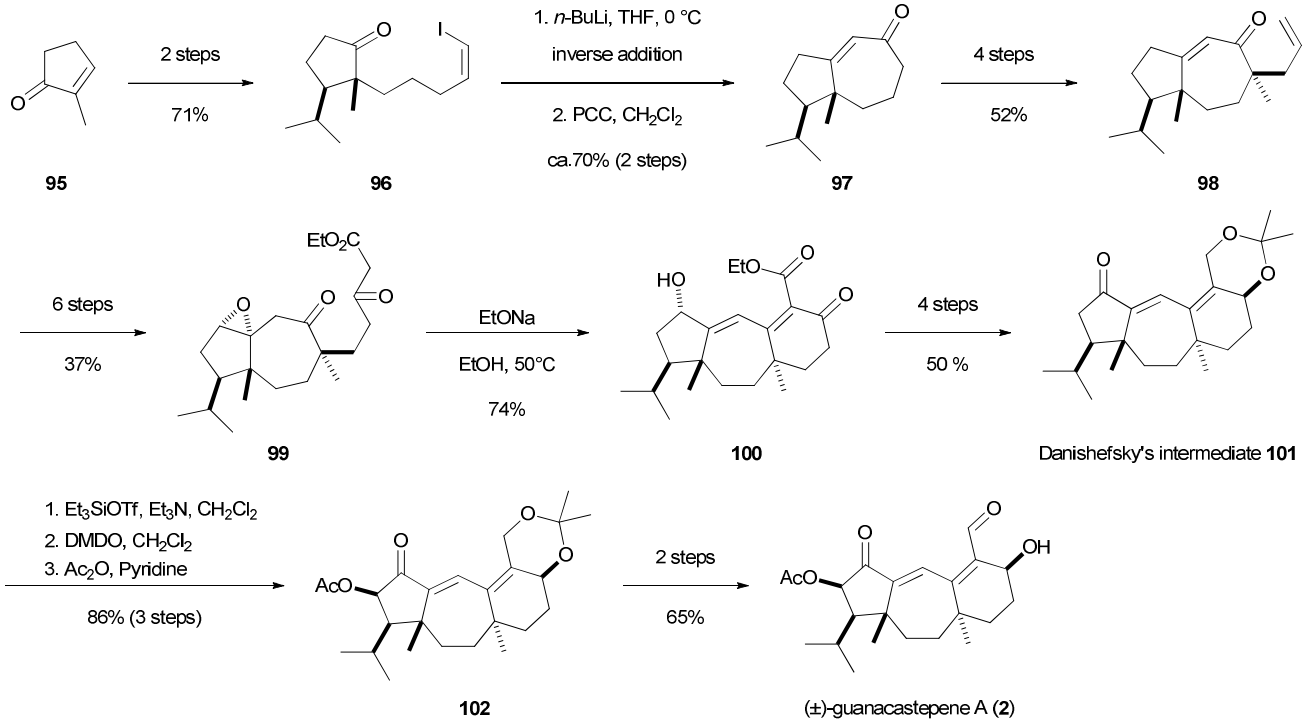
The ring C fragment was prepared by the classical resolution method using *S*-(+)-*O*-acetyl mandelic acid (Scheme 11). Cyclohexenone **124** was transformed to Danishefsky diene that underwent Diels Alder reaction with dimethyl

acetylenedicarboxylate (DMAD) giving cyclic adduct **125** in 97% yield for 2 steps. This compound **125** was further transformed to racemic allylic alcohol **126** (87% yield over two steps), which was esterified with inexpensive *O*-acetyl (*S*)-(+)-mandelic acid and the diastereoisomers were easily separated by flash column chromatography. Further exchange of mandelic ester **127** to acetic acid ester **128** was performed in 2 steps (97%).

Table 6. Different approaches to the total syntheses of guanacastepenes and heptemerones.

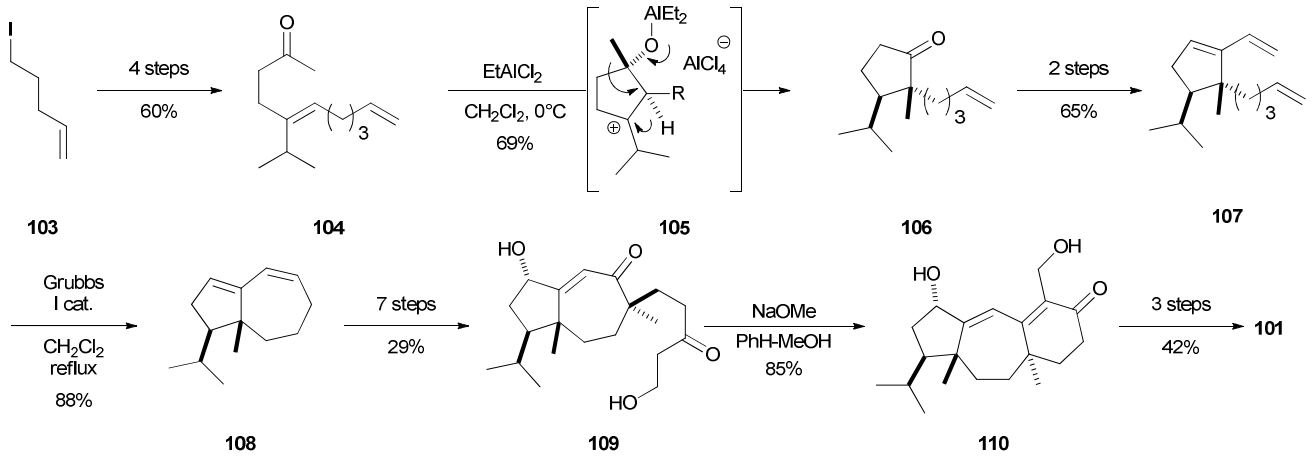
Entry	Group	Year	Compound	Methodology	Key Disconn.	Number of steps[a]	Total yield (%)	References
1.	Danishefsky	2002	(±)-guanacastepene A	Knoevenagel condensation	C3-C4	24	2.0	54, 61
2.	Snider	2002	(±)-guanacastepene A[b]	Intramolecular condensation	C3-C4	19	2.4	62
3.	Hanna	2004	(±)-guanacastepene A[b]	tandem RCM	C2-C3, C4-C5	17	-[d]	65
4.	Mehta	2005	(±)-guanacastepene C	Knoevenagel condensation	C3-C4	33	0.13	73, 74, 76
5.	Sorensen	2006	(+)-guanacastepene A[b,c] & (+)-guanacastepene E[c]	[2+2]-cycloaddition fragmentation	C10-C11	18 22	6.4 2.6	67, 68
6.	Yang	2006	(±)-C8-*epi*-guanacastepene O	IMDA	C3-C8, C4-C5	16	1.9	77
7.	Overman	2006	(+)-guanacastepene N	7-*endo*-Heck cyclisation	C2-C3	24	2.0	81
8.	Trauner	2006	(-)-heptemerone B[c] & (-)-guanacastepene E[c]	electrochemical oxidation	C1-C2	17 18	3.2 0.88	30
9.	Wicha	2010	(±)-heptemerone G & (±)-guanacastepene A[b]	Knoevenagel condensation	C3-C4	38 34	4.0 6.9	71
10.	Carreira	2011	(±)-guanacastepene N (±)-guanacastepene O	cycloinsertion fragmentation	C2-C3, C8-C9	23 23	0.09 0.17	83

[a]longest sequence; [b]formal total synthesis; [c]asymmetric; [d]yield not available

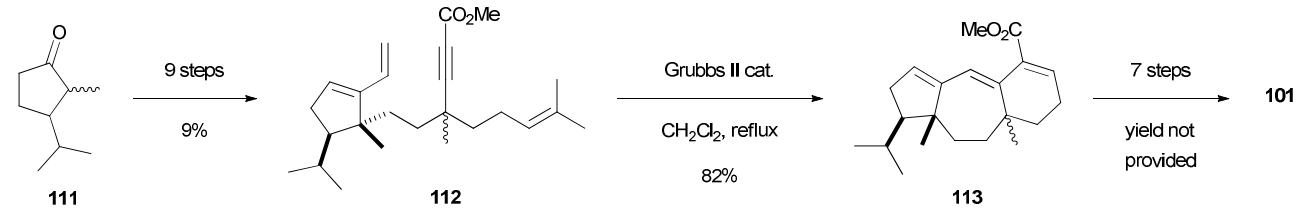


Scheme 7. First total synthesis of (±)-guanacastepene A (**2**) by Danishefsky and co-workers. PCC = pyridinium chlorochromate; DMDO = dimethyldioxirane.

Construction of the central seven-membered ring commenced by a Stille coupling under Corey conditions (CuCl additive) which unified allylic acetate **128** with stannane **123** and furnished cycloaddition substrate **129** in 91% yield (Scheme 12). Allylic mandelate **127** was also a good substrate for this reaction, slightly diminishing yield to 78%. The irradiation-mediated intramolecular [2 + 2]-cycloaddition between pendant olefin and the tetrasubstituted cyclopentene double bonds of **129** proved exclusively adduct **130** in 82% yield. Observed diastereofacial selectivity is enforced by the presence of the isopropyl group which largely dictates the configuration at the second all carbon quaternary centre providing the desired [2 + 2] adduct **130**.

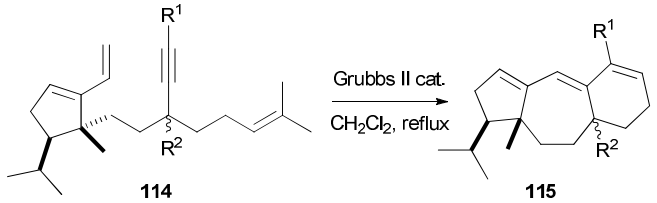


Scheme 8. Snider's formal synthesis of (±)-guanacastepene A (**2**). Grubbs I cat. = $Cl_2(PCy_3)_2Ru{=}CHPh$.



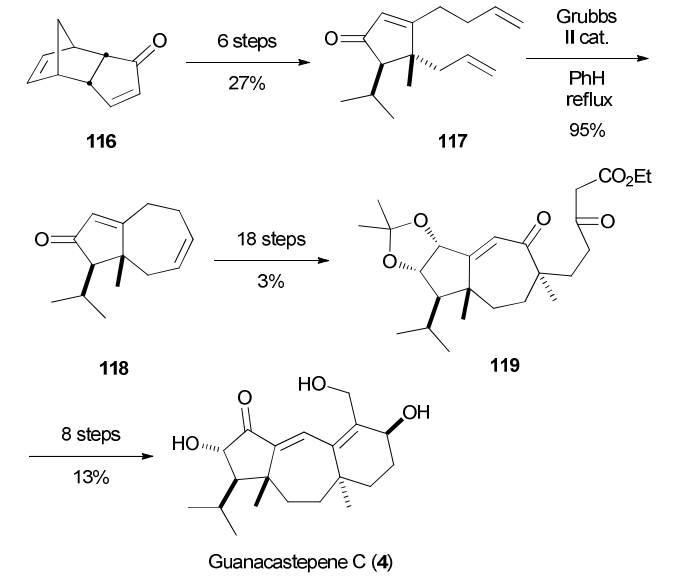
Scheme 9. Hanna's formal synthesis of (±)-guanacastepene A (**2**). Grubbs II cat. = $Cl_2(PCy_3)(NHC)Ru{=}CHPh$.

Table 7. Tandem RCM of dienynes **114a-e**. Grubbs II cat. = $Cl_2(PCy_3)(NHC)Ru{=}CHPh$.).

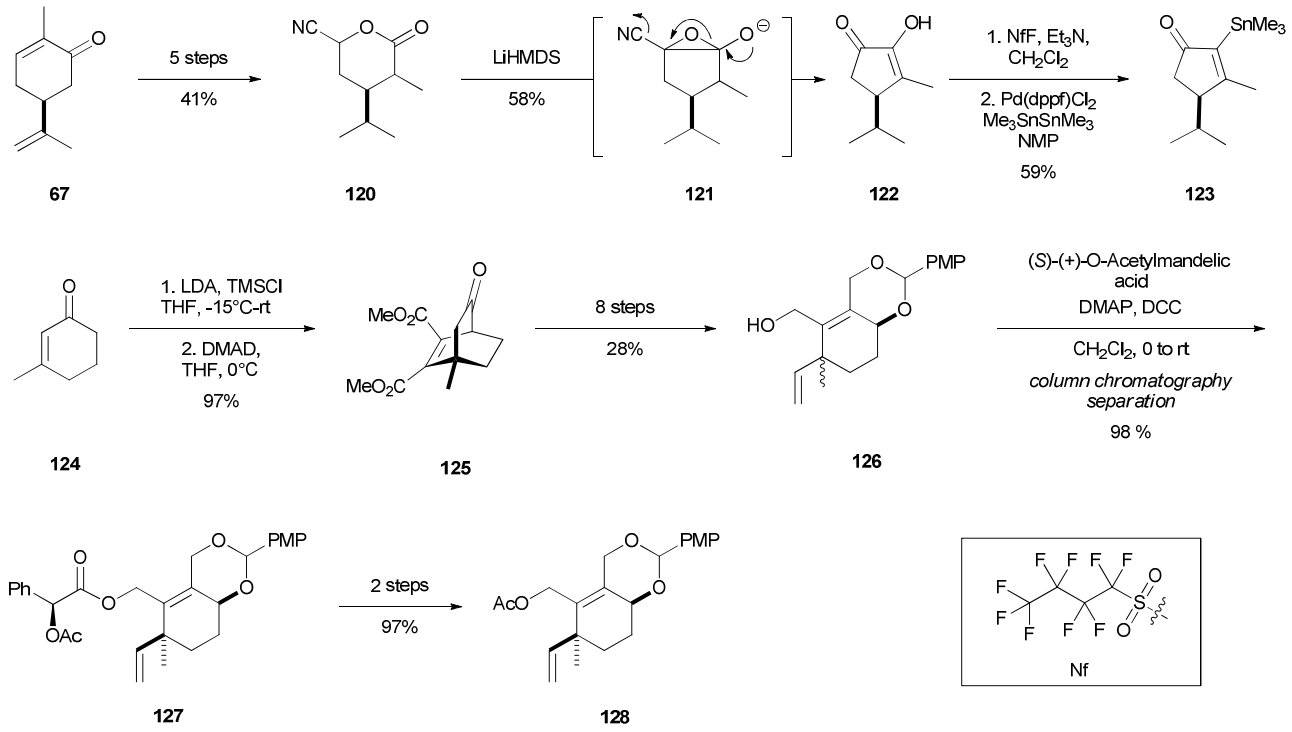


Entry	R^1	R^2	Substrate	Product	Yield
1.	H	$OSiEt_3$	**114a**	**115a**	81%
2.	Me	$OSiEt_3$	**114b**	**115b**	70%
3.	TMS	$OSiEt_3$	**114c**	**115c**	n.r.
4.	CO_2Me	$OSiEt_3$	**114d**	**115d**	93%
5.	CO_2Me	H	**114e**	**115e**	78%

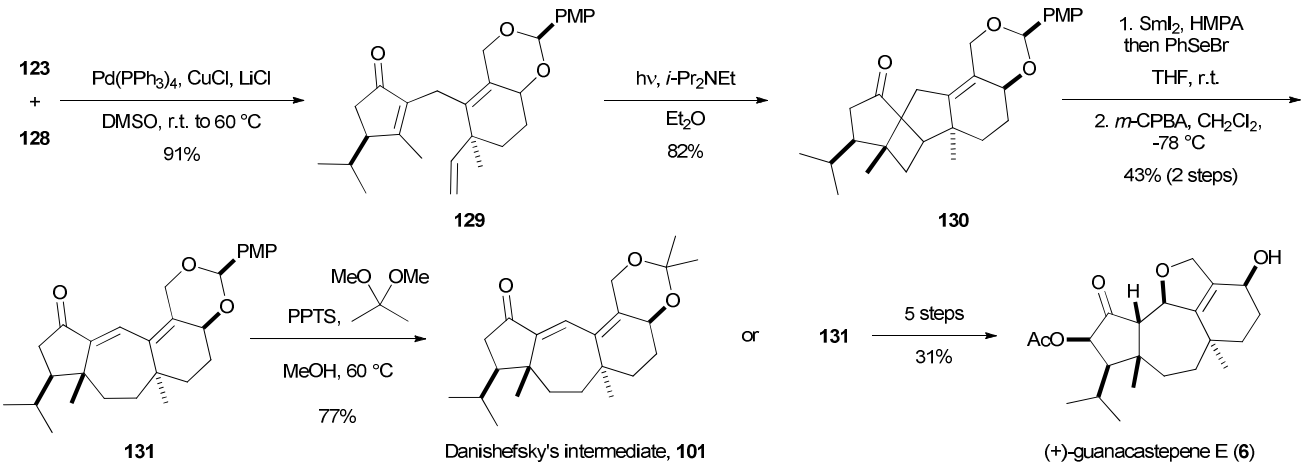
A selective reductive fragmentation of ketone **130** was achieved with samarium diiodide and the resulting putative samarium enolate was trapped with phenylselenenyl bromide giving the corresponding organoselenide that was oxidised with *meta*-chloroperoxybenzoic acid (*m*-CPBA) and eliminated to generated the complete tricyclic [5-7-6] ring system of the guanacastepenes **131** in 43% overall yield. Enone **131** was transformed to advanced Danishefsky's intermediate **101** by exchange of the benzylidene acetal to the isopropylidene ketal of **101** completing the formal synthesis of (+)-guanacastepene A (**2**). From tricycle **131**, Sorensen also performed the first total synthesis of (+)-guanacastepene E (**6**) in five steps with 31% yield.



Scheme 10. Mehta's total synthesis of (±)-guanacastepene C (**4**). Grubbs II cat. = $Cl_2(PCy_3)(NHC)Ru{=}CHPh$.

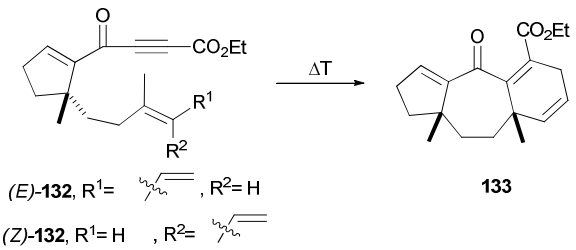


Scheme 11. Sorensen's asymmetric synthesis of A and C ring fragments of guanacastepenes. DCC = N,N'-dicyclohexylcarbodiimide; DMAD = dimethyl acetylenedicarboxylate; DMAP = 4-dimethylaminopyridine; dppf = 1,1'-bis(diphenylphosphino ferrocene); LDA = lithium diisopropylamide; LiHMDS = lithium bis(trimethylsilyl)amide; Nf = nonafluorobutanesulfonate; NMP = N-methyl-2-pyrrolidone; PMP = *para*-methoxypheny.



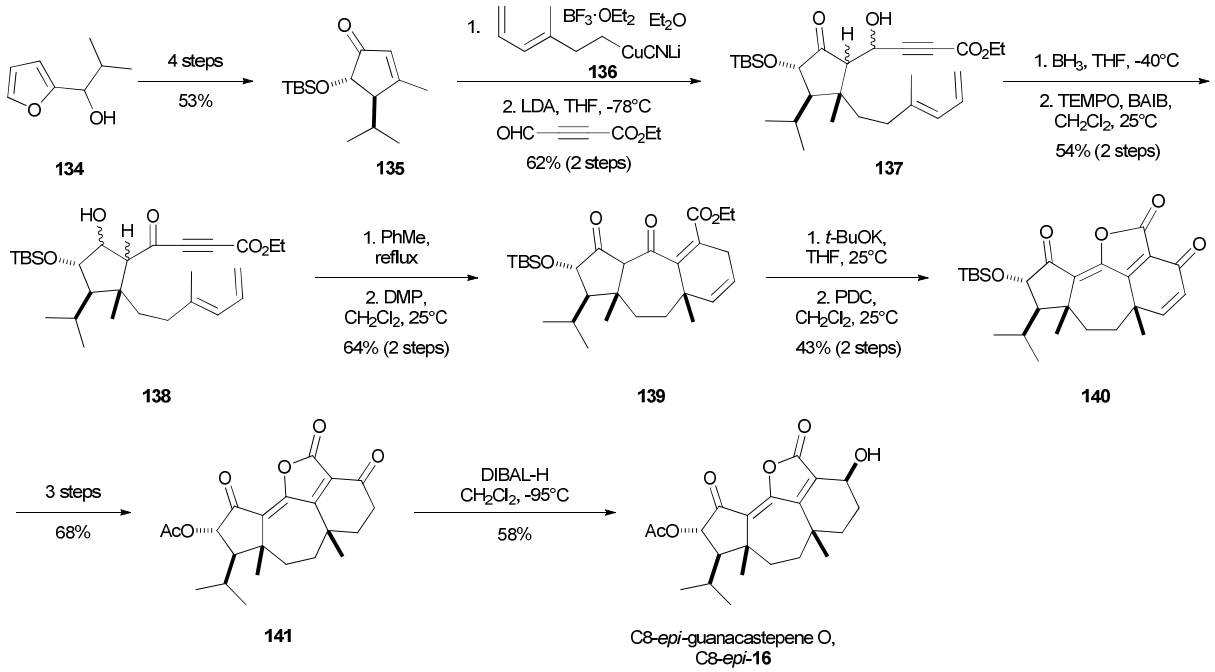
Scheme 12. Sorensen's asymmetric formal synthesis of (+)-guanacastepene A (**2**) and total synthesis of (+)-guanacastepene E (**6**).DMSO = dimethyl sulfoxide; HMPA = hexamethylphosphoramide; *m*-CPBA = *meta*-chloroperoxybenzoic acid; PPTS = pyridinium *p*ara-toluenesulfonate.

Yang and co-workers developed an intramolecular Diels-Alder (IMDA) strategy for the construction of the tricyclic core of guanacastepenes (Scheme 13).[77, 78] Although this approach is attractive in light of its concise and convergent nature leading to the fast construction of the guanacastepene skeleton, the IMDA reaction of *E*- or *Z*-precursors *E*-**132** or *Z*-**132** led to formation of thermodynamically controlled product **133** with the inverted stereochemistry of C8 all carbon quaternary centre during the model studies.

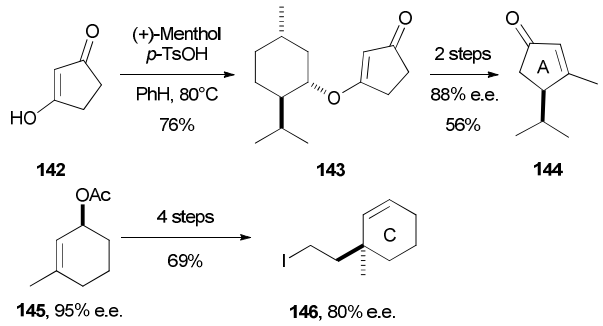


Scheme 13. Yang and co-workers IMDA strategy for the construction of the tricyclic core of guanacastepenes.

As presented in Scheme 14, this approach was further applied for the total synthesis of C8-*epi*-guanacastepene O, C8-*epi*-(**16**). Furane **134** was transformed into cyclopentenone **135** corresponding to the ring A of the guanacastepene skeleton, in four steps with 53% yield. A conjugate addition of cyanocuprate **136** to **135** followed by the aldol reaction produced propargylic alcohol **137** as a mixture of diastereoisomers in 62% yield for 2 steps. Further chemoselective reduction/oxidation reactions using BH_3 and (2,2,6,6-tetramethylpiperidin-1-yl)oxy(TEMPO)/bis(acetoxy) iodobenzene (BAIB) gave the substrate for the IMDA reaction, ketone **138** (54%). Similarly to model studies, refluxing of **138** afforded expected guancastepene core with C8-epimeric stereocentre that was oxidized with Dess-Martin periodinane (DMP) to yield a dione **139** in 64% yield. The construction of additional lactone ring was achieved under the catalytic action of *t*-BuOK and further pyridinium dichromate (PDC) oxidation installed the required keto function at C5-position. Lactone **140** thus obtained in 43% yield for two steps. Further protecting group manipulation afforded compound **141** (68%, 3 steps) which was treated with diisobutylaluminium hydride (DIBAL-H) to region- and stereoselectively reduce C5-keto function furnishing C8-*epi*-guanacastepene O, C8-*epi*-**16** in 58% yield.



Scheme 14. Yang's total synthesis of (±)-C8-*epi*-guanacastepene O (**16**). BAIB = bis(acetoxy)iodobenzene; DIBAL-H = diisobutylaluminium hydride; DMP = Dess-Martin periodinane; LDA = lithium diisopropylamide; PDC = pyridinium dichromate; TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxy.

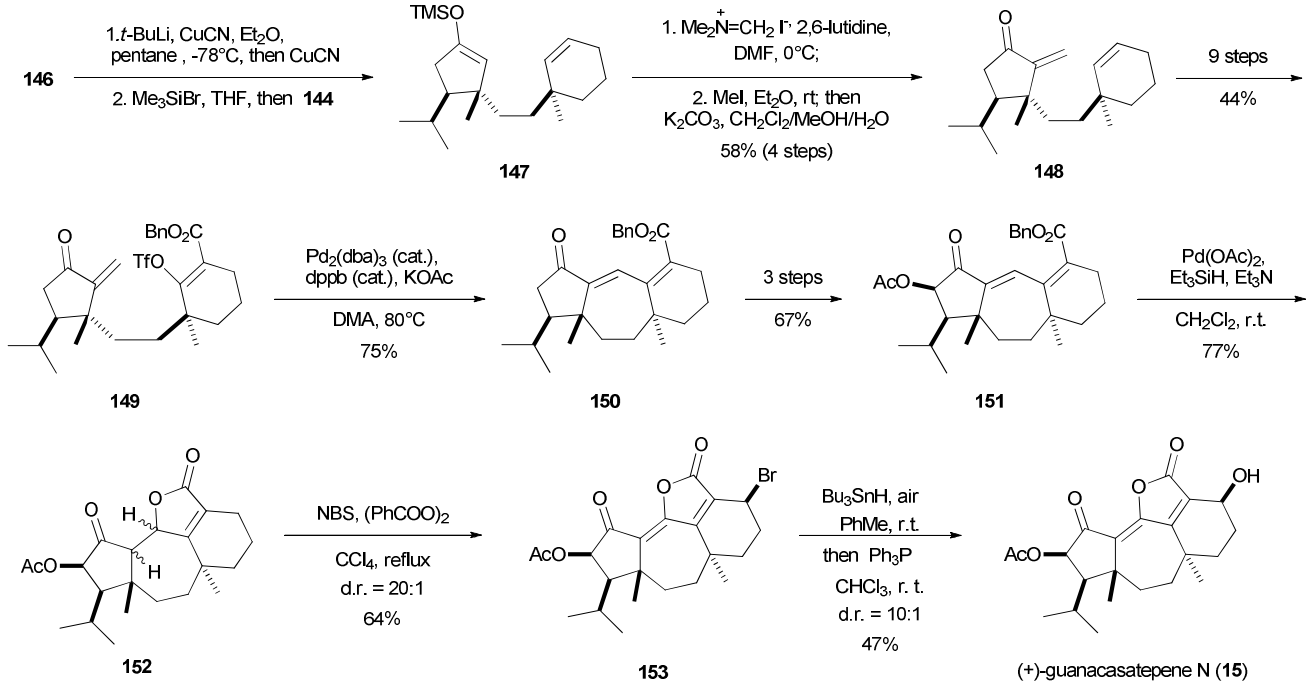


Scheme 15. Overman's asymmetric preparation of five and six membered ring portions of (+)-guanacastepene N (**15**). *p*-TsOH = *p*-toluenesulfonic acid.

In 2006, Overman's group performed the first asymmetric total synthesis of (+)-guanacastepene N (**15**).[81] This convergent synthesis used a rare 7-*endo* Heck cyclisation to close the central ring of the guanacastepene core as outlined in Schemes 15 and 18. The five-membered ring fragment **144** was obtained from dienone **142** using cheap (+)-menthol as a means to control the stereochemical outcome of the Stork-Danheiser reaction of **143** and to separate the formed diastereoisomers by HPLC. Optically active (*R*)-3-methylcyclohex-2-yl acetate (**145**) was prepared in 95% e.e. by lipase-catalysed kinetic resolution of racemic 3-methyl-2-cyclohexen-1-ol. The C8 quaternary centre of iodide **146** was formed by Ireland–Claisen rearrangement with erosion of enatiomeric excess (80% e.e.) and with 69% yield over 4 steps.

Linkage of five- and six-membered cyclic building blocks was achieved by means of a diastereoselective conjugate addition of the organocuprate reagent deriving from **146** to the enone **144** affording C11 all carbon quaternary centre (Scheme 16). The formed enolate was trapped as the enoxysilane **147**. Further functionalisation of the α-carbon was achieved by Eschenmoser methylenation providing exocyclic enone **148** in 58% yield from **147**. The key step of the synthesis is a Heck cyclisation. Thus, **148** was converted in nine steps in unsaturated triflate **149** with 39-44% yield. The palladium-catalysed intramolecular Heck cyclisation of dienyl triflate **149** as expected took place in

a 7-*endo* mode affording tricycle **150** in 75% yield. The installation of C13-acetoxy group was achieved by Rubottom oxidation firstly elaborated by Danishefsky (*vide supra*) and led to the fully functionalised A ring of tricycle **151**. Interestingly, the deprotection of benzyl ester of **151** was challenging and required the utilisation of $Pd(OAc)_2$ in the presence of Et_3SiH to provide all four possible diastereomers of lactone **152** (77%). Allylic bromination of lactone **152** with *N*-bromosuccinimide (NBS) and benzoyl peroxide installed a bromine atom at a position C5 with a high β-stereoselectivity (α/β=1:20) and simultaneously re-established the central unsaturation in 49-64% yield. As the authors suggested, the observed selectivity is a result of the steric influence of α-oriented pseudoaxial-methyl substituent at C8. The reinstallation of unsaturation at the C1-position likely occurred by allylic bromination followed by elimination of HBr. The retentive replacement of the α–Br substituent with OH was realised by air oxidation of the allylic radical derived from **153** using $(n\text{-Bu})_3SnH$ followed by *in situ* reduction of the corresponding peroxide intermediate with Ph_3P. (+)-Guanacastepene N (**15**) and its C5-epimer C5-*epi*-**15** were generated in 47% yield with α,β–diastereoselectivity of 10:1.

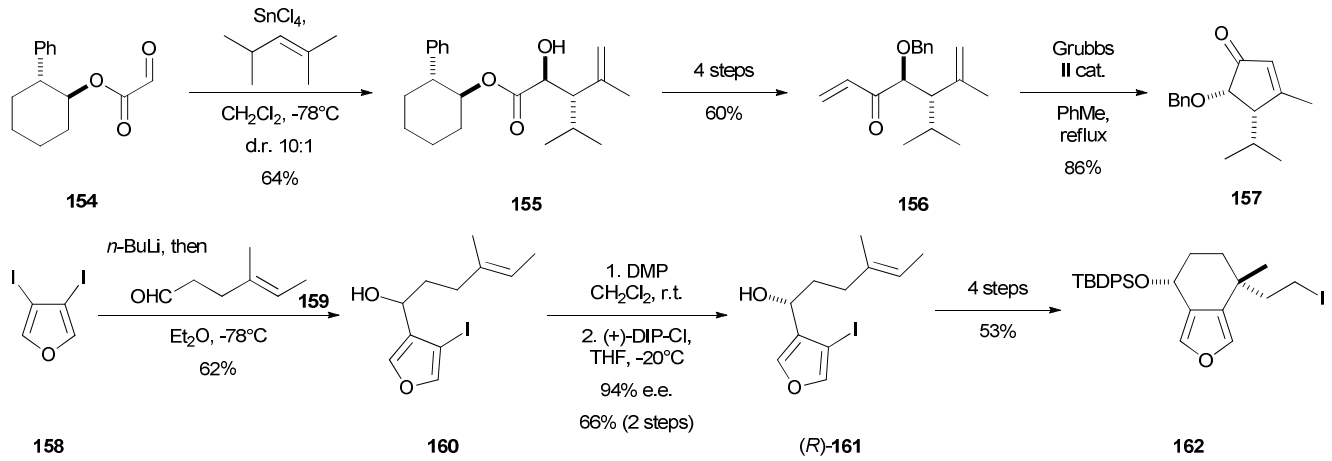


Scheme 16. Overman's total synthesis of (+)-guanacastepene N (**15**). dba = dibenzylideneacetone; DMF = dimethylformamide; DMA = dimethylacetamide; DMP = Dess-Martin periodinane; dppb = 1,4-bis(diphenylphosphino)butane NBS = N-Bromosuccinimide.

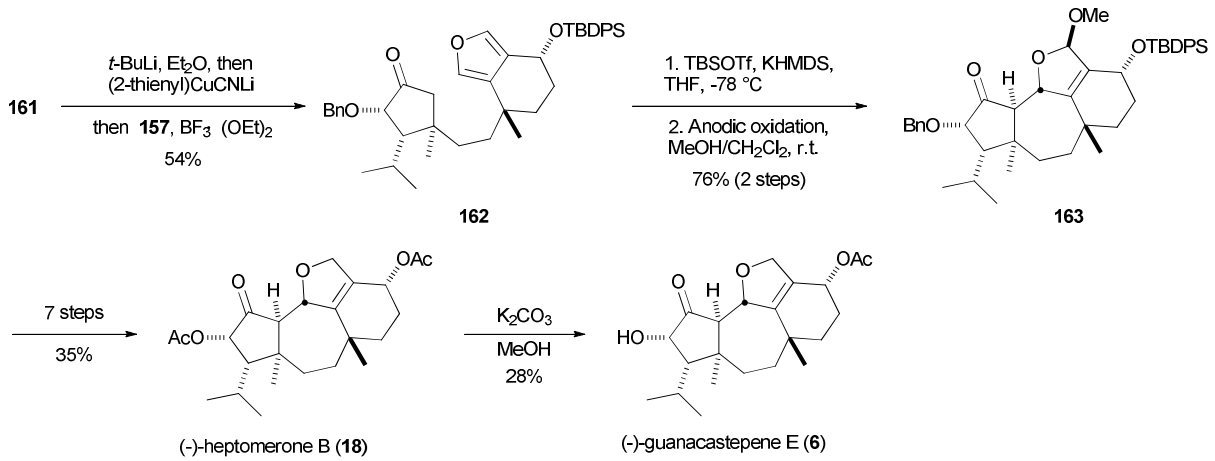
Trauner's group reported an asymmetric total syntheses of the unnatural enantiomers of (-)-heptemerone B (-)-(**18**) and (-)-guanacastepene E (-)-(**6**) (Schemes 18 and 19).[30, 79, 80] The key reaction of these concise and convergent syntheses was an uncommon electrochemical oxidation that closed the central seven-membered ring (Scheme 18). Cyclopentenone building block **157** was obtained from known chiral glyoxalate **154**. A chiral auxiliary-mediated carbonyl-ene reaction yielded the desired *anti*-diastereoisomer **155** as the major product (*anti*/*syn*=10:1) that was further transformed to enone **156** in four additional steps with 60% overall yield. Cyclisation of **156** *via* RCM catalysed by Grubbs' second generation catalyst afforded the enantiomerically pure enone **157** (86%).

The synthesis of the six-membered ring portion **161** started by the addition of mono-lithiated 3,4-diodofuran (**158**) to (*E*)-4-methylhex-4-enal (**159**) (62%). Oxidation of the obtained alcohol **160** using DMP followed by the enantioselective reduction with (+)-B-chlorodiisopinocampheylborane regenerated optically active (*R*)-**160** in 94% e.e. Palladium-catalysed intramolecular Heck reaction formed the first all carbon quaternary centre of the target molecule with a diastereomeric ratio of 5.1:1. The intermediate was further transformed in a four steps sequence to the primary iodide **161** finishing the synthesis of six-membered ring fragment of the molecule.

To link the A and C ring fragments of the molecule the authors combined the protocols of Lipshutz and Yamamoto for cuprate conjugate addition. The organocuprate arriving from **161** was added to the enone moiety of **157** in the presence of $BF_3{\bullet}Et_2O$ providing **162** in 54% yield and forming C11 all carbon quaternary stereocentre (Scheme 18). Intramolecular formation of C1-C2 bond was achieved by employing Moeller's and Wright's anodic oxidation of enoxysilane generated from **162**. This umpolung reaction coupled silyl enol ether with the furane moiety and closed the central seven-membered ring of the ketone **163** in 76% overall yield. Further elaboration of **163** afforded the unnatural enantiomer of (-)-heptemerone B (-)-(**18**) (35%) in seven steps and after methanolic hydrolysis of acetate, (-)-guanacastepene E (-)-(**6**) (28%).



Scheme 17. Trauner's asymmetric synthesis of A and C ring fragments of (-)-heptemerone B (-)-(**18**) and (-)-guanacastepene E (-)-(**6**). DMP = Dess-Martin periodinane; [(+)-DIP-Cl] = (+)-*B*-chlorodiisopinocampheylborane; Grubbs II cat. = $Cl_2(PCy_3)(NHC)Ru=CHPh$; TBDPS = *tert*-butyldiphenylsilyl.

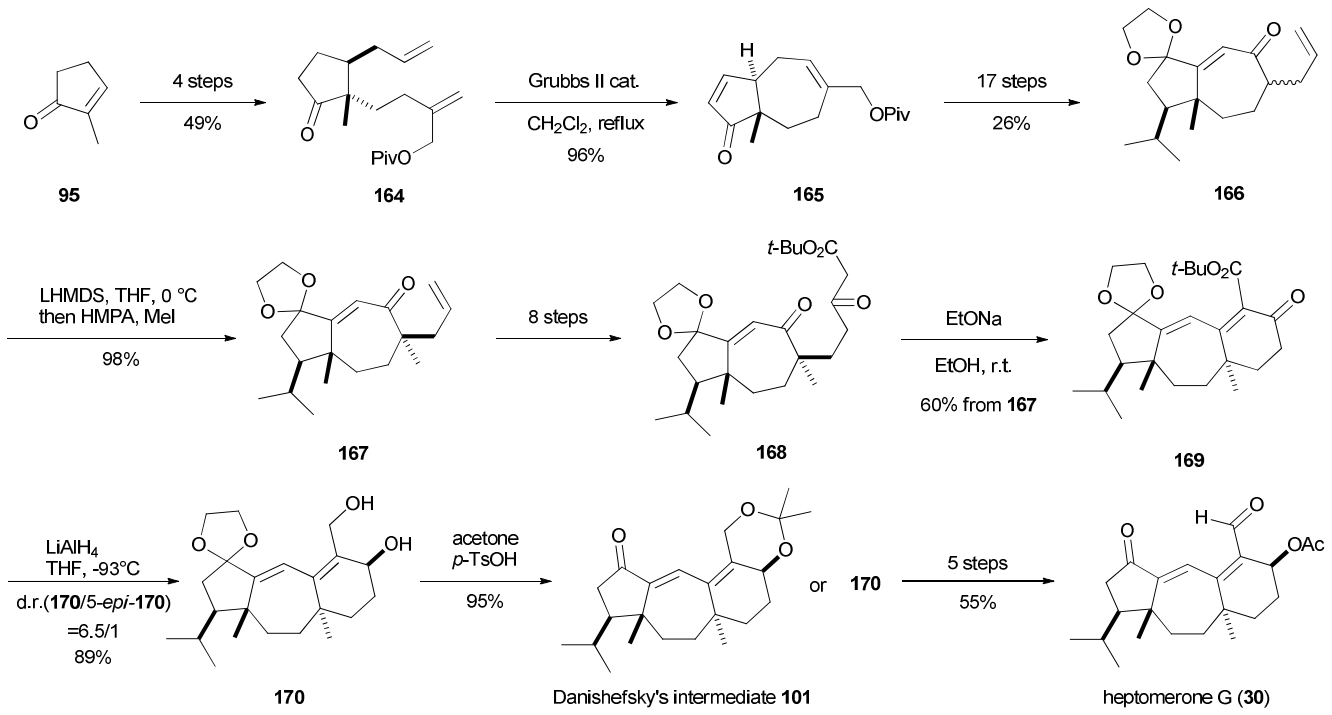


Scheme 18. Trauner's total synthesis of (-)-heptemerone B (-)-(**18**) and (-)-guanacastepene E (-)-(**6**) using aniodic oxidation as key step. KHMDS = potassium bis(trimethylsilyl)amide; TBSOTf = trimethylsilyl trifluoromethanesulfonate.

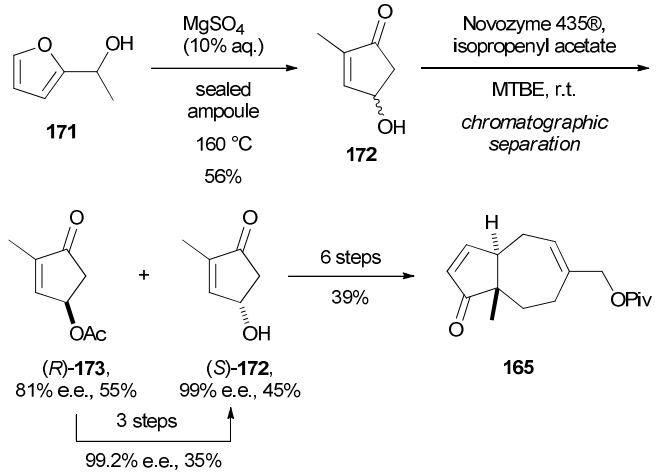
In 2010, Wicha and co-workers reported the first total synthesis of (±)-heptemerone G (**30**) and a formal total synthesis of (±)-guanacastepene A (**2**) based on Danishefsky's late-stage acetonide **101**.[70, 71] Similarly to Tius[42] and Srikrishna,[44] authors used the RCM strategy for the synthesis of hydroazulene bicyclic core **165** (Scheme 19).[72] Cyclopentanone **95** was employed as the starting material and transformed into diene **164** in 4 steps with 49% yield. Ring-closing-metathesis catalysed by Grubbs second generation catalyst formed bicycle **165** in excellent yield. Its further conversion to enone **166** was achieved in seventeen additional steps and 26% overall yield. Lithium enolate derived from **166** was successfully generated using LiHDMS and hexamethylphosphoramide (HMPA). This procedure, firstly established by Danishefsky, allowed the stereoselective installation of the methyl group of **166**.

Eight steps homologation sequence of **167** led to β-ketoester **168** that underwent the intramolecular Knoevenagel condensation and afforded tricycle **169** (60% yield over nine steps). An additional three step synthetic sequence *via* diol **170** provided Danishefsky's intermediate **101** and thus virtually completed the formal synthesis of (±)-guanacastepene A (**2**). Three steps transformation of diol **170** also allowed the first total synthesis of (±)-heptemerone G (**30**) in 55% overall yield.

In 2013, Wicha and co-workers disclosed a synthesis of the optically active hydroazulene core **165** using 2-furyl methyl carbinol (**171**) as the starting material (Scheme 20).[69] One-pot Piancatelli rearrangement–isomerisation sequence using **171** and $MgSO_4$ (10% aq.) at 160°C provided enone **172** in 56% yield. The enzymatic kinetic resolution of *rac*-**172** with Novozym 435® and isopropenyl acetate afforded (*S*)-**172** in 99% e.e. and 45% yield after column chromatography separation. Acetate (*R*)-**173** obtained in 81% ee and 55% yield, was converted into optically active **172** by an adapted Tanis three step sequence based on a hydrolysis, Mitsunobu inversion and an enantiomeric enrichment enhancing the total yield of (*S*)-**172** to 80%. Optically active intermediate of previous synthesis, ketone **165** was obtained in six steps with 39% yield.



Scheme 19. Wicha's first total synthesis of (±)-heptemerone G (**30**) and formal total synthesis (±)-guanacastepene A (**2**). LHMDS = lithium bis(trimethylsilyl)amide; Grubbs II cat. = $Cl_2(PCy_3)(NHC)Ru=CHPh$; HMPA = hexamethylphosphoramide; *p*-TsOH = *para*-toluensulfonic acid.



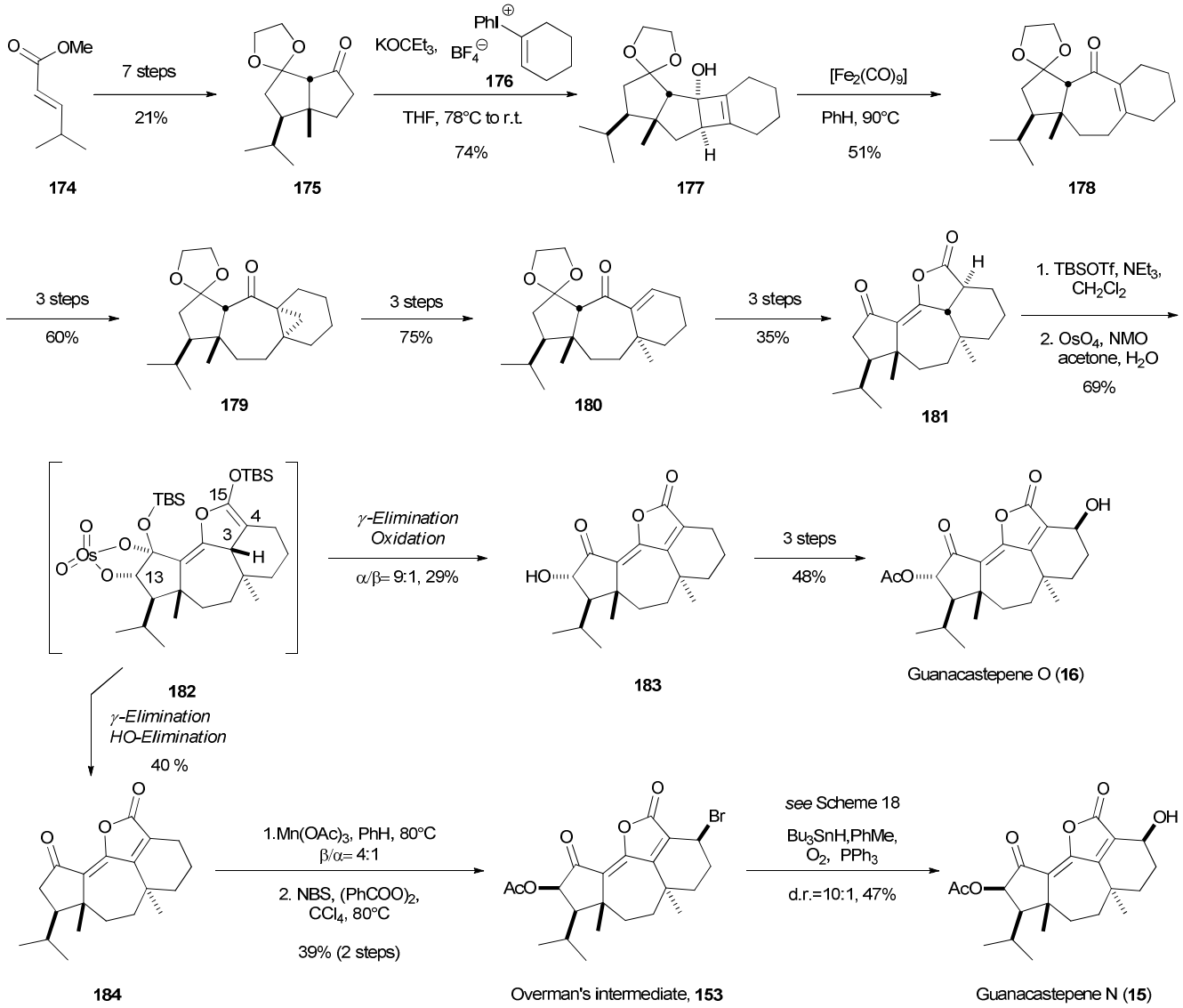
Scheme 20. Wicha's preparation of optically active hydroazulene fragment **165**. MTBE = methyl *tert*-butyl ether.

In 2011, Carreira and Gampe reported the total syntheses of (±)-guanacastepenes N (**15**) and O (**16**).[87, 82, 83] As shown in Scheme 21, the synthesis commenced with the preparation of fused cyclopentanone **175** by a sequence of seven steps that correctly installed C11 all carbon quaternary stereocentre. To obtain guanacastepene tricylic scaffold, authors employed their original annulative ring expansion cascade consisting of a one-pot addition and ring opening reactions.[87, 88] Thus, the enolate derived from **175** was reacted with cyclohexyne generated *in situ* from iodonium salt **176**. The obtained cyclobutenol **177** (74%) underwent $[Fe_2(CO)_9]$ initiated ring opening giving guancastepene tricylic core **178** in 51% yield (for further discussion see Schemes 25 and 26). The DIBAL-H reduction followed by cyclopropanation using Shi's modification of the Furukawa conditions and a re-oxidation back to the ketone stage, afforded 1:1 mixture of diastereomeric cyclopropanes **179** in 60% yield over three steps (Scheme 21). Cleavage of the cyclopropyl ring under Birch conditions installed C8 quaternary centre with correct stereochemistry and was followed by three step sequence to furnish enone **179** (75%) that was further transformed to lactone **181** in 35% yield. Treatment of **181** to TBSOTf/Et_3N afforded the corresponding *bis*-TBS-enol ether. Interestingly, exposure of this compound to OsO_4/NMO triggered the oxidative cascade reaction producing ketone **184** and α-hydroxyketone **183** in 69% overall yield. As proposed by Carreira, the postulated intermediate, osmate **182** first undergoes γ-elimination (H-C3) followed by oxidation to give **183** (29%) or HO-elimination to afford **184** (40%). Although not suggested, the formation of product **184** can also arrive from non-selective osmylation of C4-C15 olefine functionality of bis-silyl enol ether arriving from **181** followed by elimination of H-C3 proton. Similarly, the product **183** may be formed by the dihydroxylation of C13-C14 and C4-C15 olefinic bonds of the same intermediate and elimination of proton at C3. In contrast to β-selectivity of Rubottom oxidation, the installation of C13-hydroxyl group of **183** occurred with a high α-diasterofacial selectivity (α/β=4:1).

From hydroxyketone **183**, the total synthesis of guanacastepene O (**16**) was terminated in three additional steps with 48% overall yield. On the other hand, ketone **184** was transformed to guanacastepene N (**15**) *via* Overman's late intermediate **153**.

The treatment of **184** with $Mn(OAc)_3$ installed the acetoxy group at β–side (β/α=4:1, 68%) and was followed by Wohl–Ziegler bromination that gave the desired β-bromide **153** in 58% yield (see also Scheme 16).

In addition to the synthesis of (±)-guanacastepenes N (**15**) and O (**16**), Carreira and Gampe synthesised precursors of (±)-guanacastepenes D (**5**) and H (**9**), as shown in Scheme 22. The intermediate of the previous synthesis, enone **180**, was converted to five aminated diterpenoids **185-189**.[82] The reaction of **180** with Nagata's reagent (Et_2AlCN) followed by treatment with $HClO_4$ transformed intermediate nitrile, to 2:1 mixture of C4-epimers of α- and β-**185** in 16-25% yields over two steps. The diversification of the carbon scaffold **185** was achieved by the oxidation with high excess of NBS providing dienyl lactame **186** (40%) or with NCS (2.0 equiv.) giving allylic chloride **188** in 95% yield (d.r. α/β=95:5). Interestingly, the use of Me_3NPhBr_3 led to C13-bromination of lactames **185** and **186** and produced guanacastepene scaffolds **187** (d.r.=4:1, 90%) and **189** (d.r. α/β=1:1; 90%), respectively.

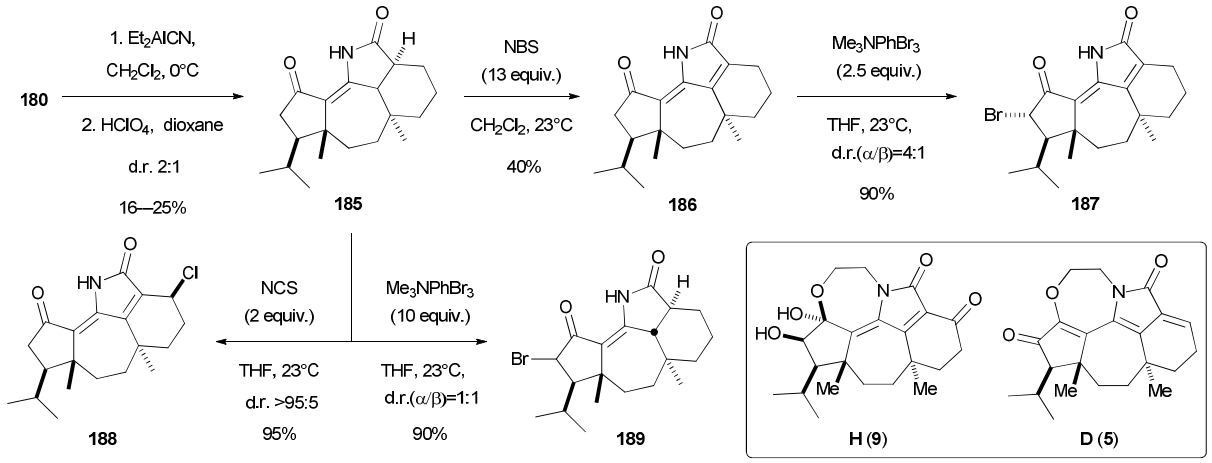


Scheme 21. Carreira's total syntheses of (±)-guanacastepenes N (**15**) and O (**16**). NBS = N-bromosuccinimide; TBSOTf = trimethylsilyl trifluoromethanesulfonate.

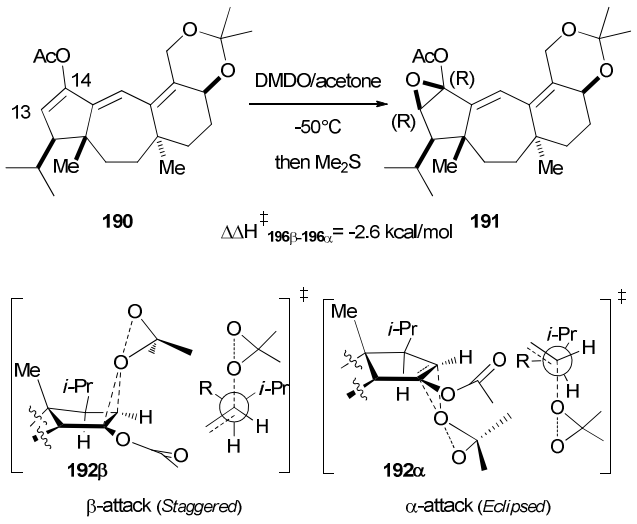
6.4 Computational Studies

Achievements in the synthesis of guanacastepenes have opened an avenue for computational research and demonstrated the necessity of their synergy. For instance, Danishefsky and co-workers employed Rubottom oxidation protocol to install C13 acetoxy function of guanacastepene A (*vide supra*, Scheme 7).[54, 58] Surprisingly, the epoxidation of silyl enol ether **190** with dimethyldioxirane (DMDO) occurred from more congested β-face providing **191** with the synperiplanar epoxy moiety to residual C12-isopropyl and C11-methyl functionalities. This intriguing stereoselectivity was a subject of computational studies performed by Houk, Danishefsky and co-workers.[89]

The corresponding transition structures and energies leading to α- and β-selectivities were calculated employing density functional theory investigations as shown in Scheme 23. Because of the eclipsing interactions, the α-epoxidation transition structure **192**α is less stable for 2.6 kcal/mol compared to staggered transition structure **192**β for β-epoxidation as shown by Newman projections. This torsional steering[90] is the most important factor and enhances the energetic difference of two transition states preferring β-epoxidation. The high asynchronicity of the formation of C14-O and C13-O bonds in the transition structures still intensifies the torsional interactions.



Scheme 22. Carreira's progress towards guanacastepenes D (**5**) and H (**9**). NCS = N-chlorosuccinimide; NBS = N-bromosuccinimide.



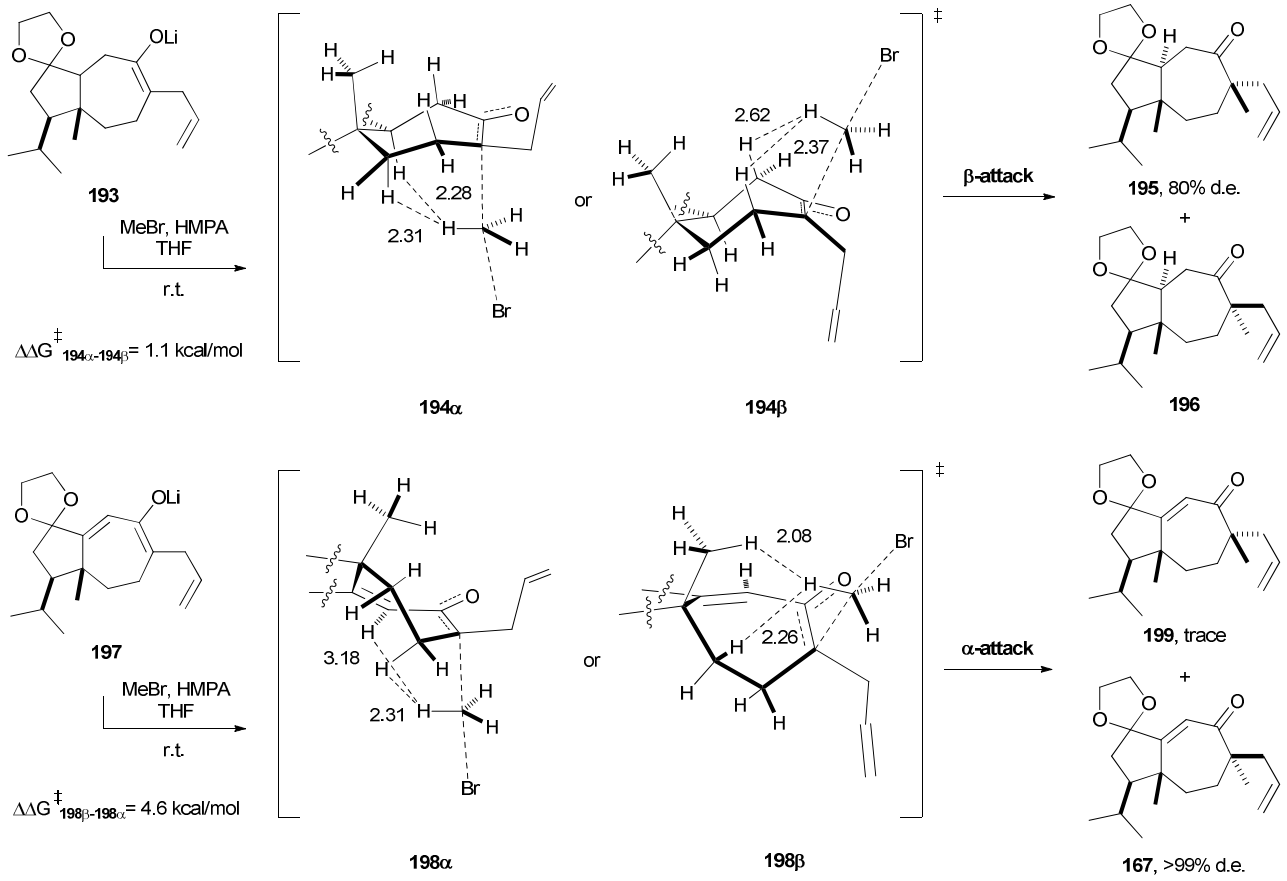
Scheme 23. The origin of facial selectivity of epoxidation of enol ether **190** as computed by Houk, Danishefsky and co-workers using the ONIOM method. DMDO = dimethyldioxirane.

In another study, Houk, Wicha and co-workers examined the origin of the stereoselectivity of alkylations of lithium enolates of hydroazulenones **193** and **197** by computational methods.[91] As shown in Scheme 24, methylation of the lithium enolates **193** and **197** proceeded with the opposite diastereofacial selectivities. While enolate **193** gives the β-methylated product **195** with unnatural *syn*-angular methyl groups in 80% d.e. and 72% yield, the reaction of enolate **197** which has an extra C1-C2 double bond, led to the exclusive formation of the α-methylated product **198** (98%). Previously, Danishefsky[54] and Mehta[74] reported the same preferential α-selectivity for intermediates closely related to hydroazulenone precursor of **197**.

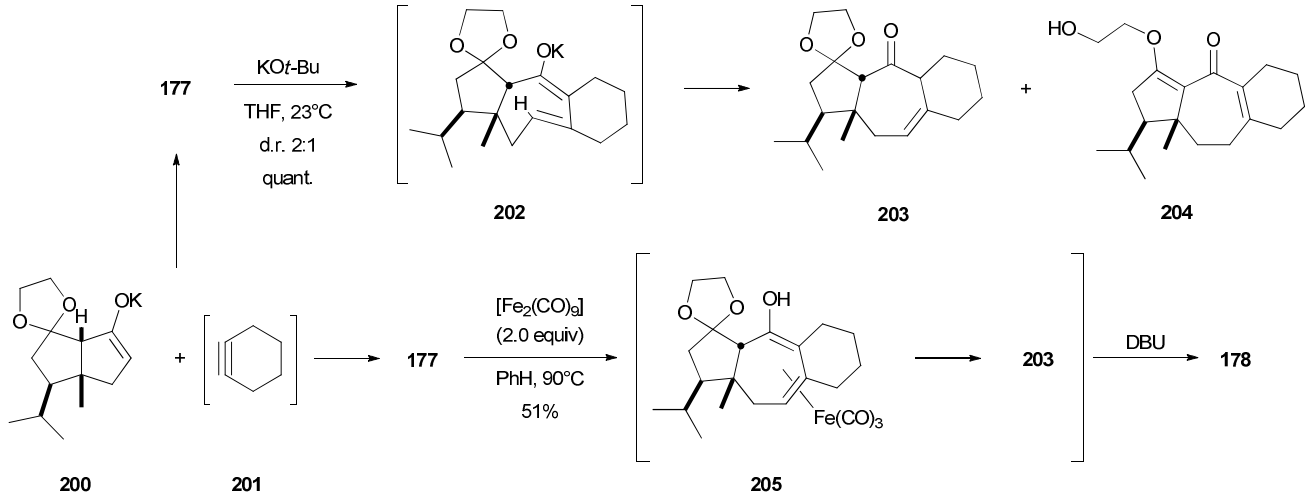
For both reactions, the steric effects rather than torsional factors were responsible for the formation of the observed products. The pseudo-chair conformation of enolate **193** was computed to be most stable. α-Attack on **193** leads to transition structure **194**α that has significant steric repulsion between an H-atom of methyl bromide and two homoallylic Hs with the distances under the sum of their van der Waals radii (2.28Å and 2.31Å *vs* 2.37Å and and 2.62Å Scheme 24). In contrast, only one steric interaction is present in the transition structure of the β-methylation **194**β, with the distance 2.37Å. Thus, the transition state for β-methylation is 1.1 kcal/mol lower in energy than the α-methylation transition state, which also corresponds to the observed diastereoselectivity d.e. (**195**/**196**)=80%. As predicted by calculations, the enolate **197** adopts the pseudo-twist-boat conformation with the C8-angular methyl on β-face of the molecule pointing towards the enolate moiety. Therefore, two major steric repulsions between the H-atom of methyl bromide and H-atoms of the substrate are present for β-alkylation with the distances 2.08 and 2.26 Å leading to exclusive α-attack of the electrophile. The transition state of α-alkylation with methyl bromide on enolate **197** was calculated to favour α-attack for $\Delta\Delta G^{\neq}_{\mathbf{202}\beta-\mathbf{202}\alpha}$= 4.6 kcal /mol (>99% d.e.).

In 2010, Carreira and Gampe reported their seminal work on the insertion of cyclohexynes into cyclic ketones leading to the formation of medium-sized, fused rings.[88] They further applied this new methodology in the synthesis of natural products (Scheme 25).[87] Specifically, the tricyclic core of guanacastepene was synthesised using *in situ* generated enolate **200** and cyclohexyne **201**.[82, 83] When cyclobutenol **177**,

acquired as a single diastereomer, was treated with *t*-BuOK, a 2:1 mixture of enones **203** and **204** was obtained. The authors proposed that the potassium alkoxide of **177** undergoes torquoselective[90] electrocyclic ring opening *via* intermediate **202** to afford

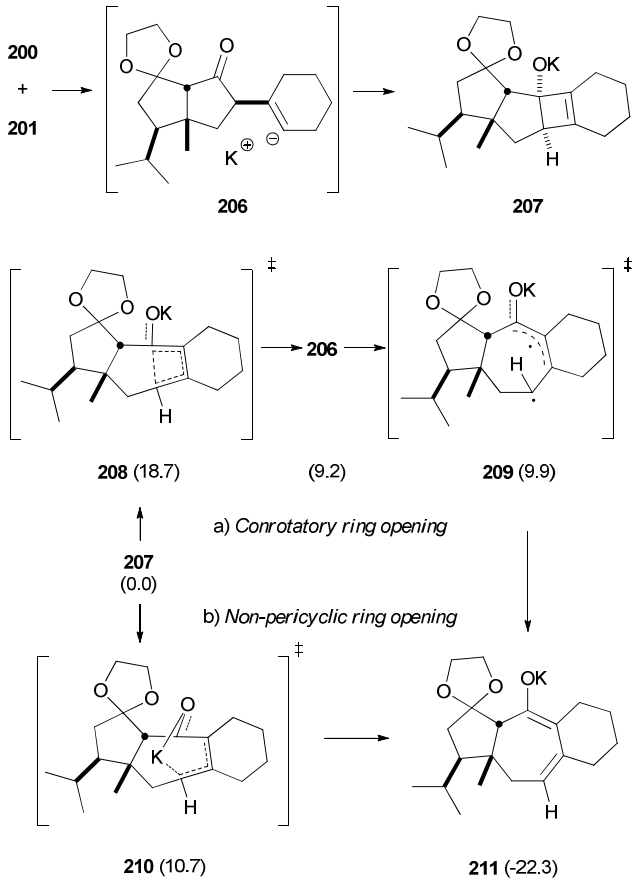


Scheme 24. Sterically controlled alkylations of lithium enolates of hydroazulenones **193** and **197**, as computed by Houk, Wicha and co-workers, and their corresponding free energies at 298K. using B3LYP/6-31G* method and solvent correction employing the CPCM polarizable conductor calculation model as implemented in Gaussian 03 at 298K. For **198**α, **198**β, methanol was specified as the solvent and for **202**α, **202**β, THF. Distances given in Å. HMPA = hexamethylphosphoramide.



Scheme 25. Carreira and Gampe's insertion of cyclohexynes into cyclic ketones in the synthesis of the tricyclic core of guanacastepenes.

non-conjugated enone **203**. The *trans-cis* isomerisation of strained *trans*-cycloheptadiene **202** and protonation furnished **203** or tautomerisation to C1 gave rise to dienone **204**. To avoid the formation of a mixture of products, Carreira and Gampe subjected cyclobutenol **177** to iron-promoted electrocyclic ring opening that occurred more selectively *via* the intermediacy of $Fe(CO)_3$-cyclobutene complex **205**, which afforded enone **203**. Further treatment of **203** by DBU exclusively gave the desired enone **178**. In 2012, the mechanism of this annulative cascade reaction was a subject of the computational studies performed by Houk and Sader.[92] B3LYP and M06−2X calculations of potential energy surface revealed a stepwise [2+2] cycloaddition of cyclohexyne **201** to the enolate **200** *via* intermediacy of vinyl anion **206** (Scheme 26). The first step of the reaction, nucleophilic attack of the enolate **200** on cyclohexyne **201** occurs without an activation barrier and is highly exothermic with a ΔH of −36 to −48 kcal/mol, while the second, the ring closure to cyclobutene alkoxide, has an activation energy of just 2−5 kcal/mol with exothermicity of 6−7 kcal/mol as calculated for closely related model systems.



Scheme 26. Mechanistic pathways of the insertion of cyclohexynes **201** into cyclic ketones **200** as calculated by Houk and Sader using B3LYP/6-31G(d) method. Values enclosed in parentheses are thermal energies, ΔH, shown in kcal/mol.

Theoretically, the ring opening of potassium cyclobutene alkoxide **207** to the guanacastepene core **211** may occur by torquoselective electrocyclic reaction in thermally allowed conrotatory or thermally forbidden disrotatory mode. The third distinct mechanistic pathway is based on the non-electrocyclic cleavage of C2−C9 bond. The conrotatory reaction of potassium alkoxide **207** gives a *trans*-cycloheptadiene intermediate **202** that is 9 kcal/mol less stable than starting potassium alkoxide **207** with an activation barrier of 19 kcal/mol (transition structure **208**). Further *trans-cis* isomerisation of *trans*-**198** to *cis*-**211** cycloheptadiene occurs with an activation energy of less than 1 kcal/mol. On the other hand, non-pericyclic mechanistic pathway *via* transition structure **210** directly produces *cis*-**211** cycloheptadiene that is 22 kcal/mol more stable than the starting potassium alkoxide **207**. The activation barrier of non-pericyclic mechanistic pathway is only 11 kcal/mol, leading to the conclusion that a more stable disrotatory product can be formed directly through this pathway. A truly thermally forbidden disrotatory process has a planar transition structure that was shown to be 19 kcal/mol higher in energy than the allowed conrotatory transition structure, as calculated for the model system.

7 Conclusions

Traditionally, natural products or natural product-like compounds have been one of the major resources for the generation of new drugs and their current demand for pharmaceutical purposes remains high. Natural products have frequently played an important role in deciphering processes of biological interest. Their synthesis have often led to the development of new methodologies with broad synthetic applications.

As presented by this review, the interdisciplinary research related to guanacastepenes has been constantly increasing. New compounds bearing neodolastane skeleton **1**were isolated and characterised from fungal and marine resources. Their therapeutic properties still have to be investigated in detail. In this light, guanacastepenes have been an interesting target for many synthetic groups and they have opened a door for the development of new and innovative methodologies for the construction of C_5-C_7-C_6 tricyclic skeletons. By undertaking a survey towards their synthesis, fundamental stereochemical and mechanistic questions were answered. To conclude, guanacastepenes are a recent example of how natural products stimulate progress in research in different fields and in general, the acquirement of valuable experimental and theoretical knowledge.

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9 Notes and References

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1. O. Potterat and M. Hamburger, in *Natural Compounds as Drugs Volume I*, eds. F. Petersen and R. Amstutz, Birkhäuser Basel, 2008, vol. 65, pp. 45-118.
2. D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2007, **70**, 461-477.
3. G. M. Cragg, P. G. Grothaus and D. J. Newman, *J. Nat. Prod.*, 2014, **77**, 703-723.
4. F. E. Koehn and G. T. Carter, *Nat. Rev. Drug Discovery*, 2005, **4**, 206-220.
5. D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2012, **75**, 311-335.
6. L. Ruzicka, *Experientia*, 1953, **9**, 357-367.
7. P. M. Dewick, *Medicinal Natural Products - A Biosynthetic Approach.*, 3 edn., John Willey & Sons Ltd, Chichester, UK, 2009.
8. Chapman and Hall/CRC Press, Dictionary of Natural Products on CD-Rom, London, 2009.
9. J. R. Hanson, *The Chemistry of Fungi*, The Royal Society of Chemistry, Cambridge, 2008.
10. J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro and M. R. Prinsep, *Nat. Prod. Rep.*, 2013, **30**, 237-323.
11. R. A. Hill, *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.*, 2012, **108**, 131-146.
12. R. A. Hill, *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.*, 2013, **109**, 146-166.
13. J. M. Kornprobst, *Substances naturelles d'origine marine : chimiodiversité, pharmacodiversité, biotechnologies*, Lavoisier, Paris, 2005.
14. J. R. Hanson, *Nat. Prod. Rep.*, 2013, **30**, 1346-1356.
15. M. Hiersemann and H. Helmboldt, in *Natural Product Synthesis I*, Springer Berlin Heidelberg, 2005, vol. 243, pp. 73-136.
16. S. F. Brady, M. P. Singh, J. E. Janso and J. Clardy, *J. Am. Chem. Soc.*, 2000, **122**, 2116-2117.
17. S. F. Brady, S. M. Bondi and J. Clardy, *J. Am. Chem. Soc.*, 2001, **123**, 9900-9901.
18. M. Mischne, *Curr. Org. Synth.*, 2005, **2**, 261-279.
19. M. Hiersemann, *Nachr. Chem.*, 2006, **54**, 29-33.
20. S. V. Maifeld and D. Lee, *Synlett*, 2006, **17**, 1623-1644.
21. T. J. Maimone and P. S. Baran, *Nat. Chem. Biol.*, 2007, **3**, 396-407.
22. A. G. Invernizzi, G. Vidari and P. Vita-Finzi, *Tetrahedron Lett.*, 1995, **36**, 1905-1908.
23. J. MacMillan and M. H. Beale, in *Isoprenoids Including Carotenoids and Steroids*, eds. O. Meth-Cohn, D. Barton and K. Nakanishi, Elsevier Science B.V., Amsterdam, 1999, vol. 2, pp. 217-243.
24. C. Valdivia, M. Kettering, H. Anke, E. Thines and O. Sterner, *Tetrahedron*, 2005, **61**, 9527-9532.
25. R. Liu and J.-K. Liu, *Heterocycles*, 2009, **78**, 2565-2570.
26. V. Smyrniotopoulos, C. Vagias, C. Bruyère, D. Lamoral-Theys, R. Kiss and V. Roussis, *Bioorg. Med. Chem.*, 2010, **18**, 1321-1330.
27. Y.-X. Ou, Y.-Y. Li, X.-M. Qian and Y.-M. Shen, *Phytochemistry*, 2012, **78**, 190-196.
28. Y. Liu, Y. Li, Y. Ou, S. Xiao, C. Lu, Z. Zheng and Y. Shen, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5059-5062.
29. Y. Liu, C. Lu and Y. Shen, *Phytochem. Lett.*, 2014, **7**, 161-164.
30. A. K. Miller, C. C. Hughes, J. J. Kennedy-Smith, S. N. Gradl and D. Trauner, *J. Am. Chem. Soc.*, 2006, **128**, 17057-17062.
31. M. K. Leong, V. S. Mastryukov and J. E. Boggs, *J. Mol. Struct.*, 1998, **445**, 149-160.
32. G. R. Pettit, R. H. Ode, C. L. Herald, R. B. Von Dreele and C. Michel, *J. Am. Chem. Soc.*, 1976, **98**, 4677-4678.
33. C. B. Rao, K. C. Pullaiah, R. K. Surapaneni, B. W. Sullivan, K. F. Albizati, D. J. Faulkner, C. He and J. Clardy, *J. Org. Chem.*, 1986, **51**, 2736-2742.
34. H.-J. Borschberg, *Zur Biogenese des Sordarins*, Eidgenossischen Technischen HochschuIe, Zürich, 1975.
35. C. Ireland, D. J. Faulkner, J. Finer and J. Clardy, *J. Am. Chem. Soc.*, 1976, **98**, 4664-4665.
36. L. Jenny and H.-J. Borschberg, *Helv. Chim. Acta*, 1995, **78**, 715-731.
37. A. D. Rodríguez, E. González and C. Ramírez, *Tetrahedron*, 1998, **54**, 11683-11729.
38. M. P. Singh, J. E. Janso, S. W. Luckman, S. F. Brady, J. Clardy, M. Greenstein and W. M. Maiese, *J. Antibiot.*, 2000, **53**, 256-261.
39. M. Kettering, C. Valdivia, O. Sterner, H. Anke and E. Thines, *J. Antibiot.*, 2005, **58**, 390-396.
40. P. Magnus and C. Ollivier, *Tetrahedron Lett.*, 2002, **43**, 9605-9609.
41. P. Magnus, M. J. Waring, C. Ollivier and V. Lynch, *Tetrahedron Lett.*, 2001, **42**, 4947-4950.
42. A. Nakazaki, U. Sharma and M. A. Tius, *Org. Lett.*, 2002, **4**, 3363-3366.
43. P. Chiu and S. Li, *Org. Lett.*, 2004, **6**, 613-616.
44. A. Srikrishna and D. H. Dethe, *Org. Lett.*, 2004, **6**, 165-168.
45. C. A. McGowan, A.-K. Schmieder, L. Roberts and M. F. Greaney, *Org. Biomol. Chem.*, 2007, **5**, 1522-1524.
46. T. M. Nguyen, R. J. Seifert, D. R. Mowrey and D. Lee, *Org. Lett.*, 2002, **4**, 3959-3962.
47. T. M. Nguyen and D. Lee, *Tetrahedron Lett.*, 2002, **43**, 4033-4036.
48. X. Du, H. V. Chu and O. Kwon, *Tetrahedron Lett.*, 2004, **45**, 8843-8846.
49. X. Du, H. V. Chu and O. Kwon, *Org. Lett.*, 2003, **5**, 1923-1926.
50. K. M. Brummond and D. Gao, *Org. Lett.*, 2003, **5**, 3491-3494.
51. Y. Oonishi, A. Taniuchi and Y. Sato, *Synthesis*, 2010, 2884-2892.
52. H. Yun, Z. Meng and S. J. Danishefsky, *Heterocycles*, 2005, **66**, 711-725.
53. H. Yun and S. J. Danishefsky, *Tetrahedron Lett.*, 2005, **46**, 3879-3882.
54. M. Mandal, H. Yun, G. B. Dudley, S. Lin, D. S. Tan and S. J. Danishefsky, *J. Org. Chem.*, 2005, **70**, 10619-10637.
55. M. Mandal and S. J. Danishefsky, *Tetrahedron Lett.*, 2004, **45**, 3827-3829.
56. M. Mandal and S. J. Danishefsky, *Tetrahedron Lett.*, 2004, **45**, 3831-3833.
57. D. S. Tan, G. B. Dudley and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2002, **41**, 2185-2188.
58. S. Lin, G. B. Dudley, D. S. Tan and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2002, **41**, 2188-2191.
59. G. B. Dudley, S. J. Danishefsky and G. Sukenick, *Tetrahedron Lett.*, 2002, **43**, 5605-5606.

60. G. B. Dudley, D. S. Tan, G. Kim, J. M. Tanski and S. J. Danishefsky, *Tetrahedron Lett.*, 2001, **42**, 6789-6791.
61. G. B. Dudley and S. J. Danishefsky, *Org. Lett.*, 2001, **3**, 2399-2402.
62. B. Shi, N. A. Hawryluk and B. B. Snider, *J. Org. Chem.*, 2003, **68**, 1030-1042.
63. B. B. Snider and B. Shi, *Tetrahedron Lett.*, 2001, **42**, 9123-9126.
64. B. B. Snider and N. A. Hawryluk, *Org. Lett.*, 2001, **3**, 569-572.
65. F.-D. Boyer, I. Hanna and L. Ricard, *Org. Lett.*, 2004, **6**, 1817-1820.
66. F.-D. Boyer and I. Hanna, *Tetrahedron Lett.*, 2002, **43**, 7469-7472.
67. W. D. Shipe and E. J. Sorensen, *J. Am. Chem. Soc.*, 2006, **128**, 7025-7035.
68. W. D. Shipe and E. J. Sorensen, *Org. Lett.*, 2002, **4**, 2063-2066.
69. K. Michalak and J. Wicha, *Synlett*, 2013, **24**, 1387-1390.
70. K. Michalak, M. Michalak and J. Wicha, *Tetrahedron Lett.*, 2010, **51**, 4344-4346.
71. K. Michalak, M. Michalak and J. Wicha, *J. Org. Chem.*, 2010, **75**, 8337-8350.
72. K. Michalak, M. Michalak and J. Wicha, *Tetrahedron Lett.*, 2008, **49**, 6807-6809.
73. G. Mehta, K. Pallavi and J. D. Umarye, *Chem. Commun.*, 2005, **41**, 4456-4458.
74. G. Mehta, J. D. Umarye and K. Srinivas, *Tetrahedron Lett.*, 2003, **44**, 4233-4237.
75. G. Mehta, J. D. Umarye and V. Gagliardini, *Tetrahedron Lett.*, 2002, **43**, 6975-6978.
76. G. Mehta and J. D. Umarye, *Org. Lett.*, 2002, **4**, 1063-1066.
77. C.-C. Li, C.-H. Wang, B. Liang, X.-H. Zhang, L.-J. Deng, S. Liang, J.-H. Chen, Y.-D. Wu and Z. Yang, *J. Org. Chem.*, 2006, **71**, 6892-6897.
78. C.-C. Li, S. Liang, X.-H. Zhang, Z.-X. Xie, J.-H. Chen, Y.-D. Wu and Z. Yang, *Org. Lett.*, 2005, **7**, 3709-3712.
79. C. C. Hughes, A. K. Miller and D. Trauner, *Org. Lett.*, 2005, **7**, 3425-3428.
80. C. C. Hughes, J. J. Kennedy-Smith and D. Trauner, *Org. Lett.*, 2003, **5**, 4113-4115.
81. S. Iimura, L. E. Overman, R. Paulini and A. Zakarian, *J. Am. Chem. Soc.*, 2006, **128**, 13095-13101.
82. C. M. Gampe and E. M. Carreira, *Chem. - Eur. J.*, 2012, **18**, 15761-15771.
83. C. M. Gampe and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2011, **50**, 2962-2965.
84. F.-D. Boyer and I. Hanna, *Eur. J. Org. Chem.*, 2006, 471-482.
85. T. Bach and J. P. Hehn, *Angew. Chem., Int. Ed.*, 2011, **50**, 1000-1045.
86. Very recently, Alexakis' group published enantioselective route to key intermediate of Danishefsky synthesis see: Germain, N.; Guénée, L.; Mauduit, M.; Alexakis, A. *Org. Lett.* 2014, **16**, 118-121.
87. C. M. Gampe and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2012, **51**, 3766-3778.
88. C. M. Gampe, S. Boulos and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2010, **49**, 4092-4095.
89. P. H.-Y. Cheong, H. Yun, S. J. Danishefsky and K. N. Houk, *Org. Lett.*, 2006, **8**, 1513-1516.
90. H. Wang and K. N. Houk, *Chem. Sci.*, 2014, **5**, 462-470.
91. H. Wang, K. Michalak, M. Michalak, G. Jimenez-Oses, J. Wicha and K. N. Houk, *J. Org. Chem.*, 2010, **75**, 762-766.
92. C. A. Sader and K. N. Houk, *J. Org. Chem.*, 2012, **77**, 4939-4948.