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A unified approach to highly functionalized clovane-type terpenoids: enantiocontrolled total synthesis of rumphellclovane E and sarinfacetamides A and B

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This study presents an enantioselective collective total synthesis of the highly functionalized clovane-type terpenoids rumphellclovane E (**4**) and, sarinfacetamides A (**5**) and B (**6**). An efficient enantio-controlled, second-generation route to an originally designed versatile intermediate (**12**/*ent*-**12**) enables the collective synthesis, including the first total synthesis of sarinfacetamides A (**5**) and B (**6**). The rapid assembly of the bicyclo[3.3.1]nonane core *via* a domino Michael–aldol reaction employing a novel acrolein surrogate under basic conditions enabled access to this key intermediate, requiring only five steps from (+) or (−)-dihydrocarvone (**18**/*ent*-**18**). We further demonstrated the versatility of this strategy through the synthesis of a structural analogue containing a furan moiety. Given the diverse biosynthetic origins of clovanes, which arise from caryophyllene or xeniaphyllane terpenoids, this synthetic strategy may prove applicable to a broader range of clovane-type terpenoids.

Introduction

Among naturally occurring organic small molecules, terpenoids have played a vital role in diverse fields of molecular science. Their three-dimensional complex carbon skeletons and inherent structural diversity offer the potential to explore sp^3-rich chemical space, leading to new horizons in drug discovery. Of the numerous terpenoids, clovane-type terpenoids have attracted significant attention from the synthetic community owing to their unique tricyclo[6.3.1.$0^{1,5}$]dodecane ring system[1] (Fig. 1a, highlighted in blue) and diverse biological activities.[2] Clovane-type terpenoids characteristically possess functional groups at C2 and C9 owing to their biosynthetic origins. They arise from caryophyllene-type terpenoids[2i,3] exemplified by (−)-caryophyllene β-oxide (**1**).[4] The acid-catalyzed opening of the C8–C9 epoxide and transannular bond formation generates bridgehead carbocation **A**. The subsequent Wagner–Meerwein rearrangement forms the C2 carbocation **B**, establishing the tricyclo[6.3.1.$0^{1,5}$]dodecane system, which is the central core of the clovane skeleton. The resulting carbocation **B** is then captured by various nucleophiles, such as alcohol, water, or ammonia, to yield the characteristic oxygen- or nitrogen-containing functionalities. Conventionally known clovane-type terpenoids rarely undergo oxidative modifications beyond those introduced by biosynthesis, and chemists have primarily focused on these C2, C9-oxygenated families[5] (*e.g.*, clovane-2,9-dione (**2**) and clovanemagnolol (**3**)). Among them, the biomimetic strategy, as demonstrated by Siegel *et al.*, is particularly concise because it enables the construction of a C2- and C9-oxidized clovane skeleton in a single step by utilizing a biomimetic cascade rearrangement.[5a]

However, in recent years, "highly functionalized" clovane-type terpenoids such as rumphellclovane E (**4**)[2g] and sarinfacetamides A (**5**) and B (**6**)[2j]—possessing additional functional groups beyond C2 and C9—have been isolated (Fig. 1a, right). Notably, sarinfacetamide A (**5**) exhibits a unique biological activity promoting ConA-induced T lymphocyte proliferation.[2j] Rumphellclovane E (**4**) contains an extra oxygen functional group at C12, likely introduced *via* enzymatic oxidation of the C2, C9-oxidized clovane skeleton. Sarinfacetamides A (**5**) and B (**6**) are derived from nanolobatine B (**7**),[6b] a xeniaphyllane-type terpenoid with an oxidized side chain at C4, through a similar biosynthetic cyclization involving nitrogen atom incorporation. Additionally, various xeniaphyllane-type terpenoids, including nanolobatin B[6b] (**7**), possess the opposite absolute configuration to most caryophyllene terpenoids.[6] Consequently, sarinfacetamides have the opposite absolute configuration to that of typical clovane-type terpenoids. Given the diversity of xeniaphyllane terpenoids[6] (*e.g.*, sinubatin B (**8**)[6f] or sinuhirfuranone A (**9**)[6g]), numerous side chain-modified clovane-type terpenoids are expected to exist (Fig. 1b). Therefore, a modular strategy that enables the diversification of side chain structures is highly valuable not only for achieving the collective synthesis of known

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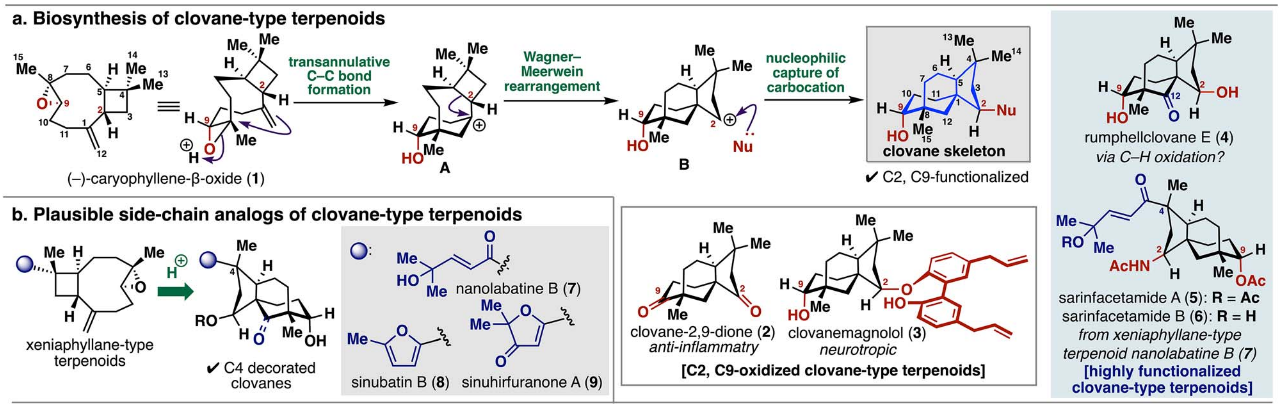


Fig. 1 Biogenesis of clovane-type terpenoids.

clovane-type terpenoids but also for paving the way towards the synthesis of structural analogues.

Despite the significance of highly functionalized clovane-type terpenoids, synthetic efforts toward their construction remain limited. As mentioned above, C2 and C9-functionalized clovane skeletons are readily available from (−)-caryophyllene β-oxide (**1**) *via* biomimetic rearrangement. Thus, C–H functionalization of caryophyllene frameworks offers a promising route to highly functionalized clovanes; however, achieving such regioselective Csp^3–H activation remains a formidable challenge (Fig. 2a). While Fu and Liu achieved a concise total synthesis of rumphellclovane E (**4**) in 2021 (ref. 7) *via* a cyclopropanation/C–C bond cleavage strategy (Fig. 2b), their approach is challenging to apply to other complex congeners such as the sarinfacetamides. Consequently, a general strategy for synthesizing clovane-type terpenoids with functionalized cores and/or side chains remains elusive.

To address this knowledge gap, we designed a potentially versatile intermediate (**12**) as a synthetic platform for diverse clovane-type terpenoids (Fig. 2c). This intermediate possesses three key features.

(1) It is accessible in both enantiospecific forms from commercially available chiral building blocks.

(2) It incorporates all the oxygen atoms (at C2, C9, and C12) present in currently known clovane-type terpenoids.

(3) It allows for the introduction of various nucleophiles at C4 of the clovane scaffold *via* conjugate addition to the enone moiety.

Previously, we reported a synthetic route to this potentially versatile intermediate (**12**) derived from (−)-carvone (**10**).[8] However, the lengthy and inefficient synthetic sequence (11 steps, 9% overall yield), which employed tedious skeletal construction and oxidative decoration, hampered the sufficient supply of **12**, resulting in limited application of **12**, and it was only used in the formal synthesis of rumphellclovane E (**4**). As a result, the complete versatility of intermediate **12** remained unexplored. In particular, the introduction of diverse side chain moieties at the C4 position—a key feature of several highly functionalized clovane derivatives—has not been achieved. Given the isolated C4-functionalized clovanes (*e.g.*, sarinfacetamides) and the potential existence of additional congeners derived from xeniaphyllanes, addressing this gap in synthetic strategy is warranted. Herein, we report an enantiocontrolled unified total synthesis of rumphellclovane E (**4**) and sarinfacetamides A (**5**) and B (**6**). A highly efficient and scalable route to access the key intermediate **12** in five steps from dihydrocarvone was enabled by a domino Michael–aldol sequence with a novel acrolein surrogate under basic conditions. This versatile intermediate enables access to all known highly functionalized clovane-type terpenoids and their structural analogues, highlighting the complete versatility of the designed intermediate for the first time.

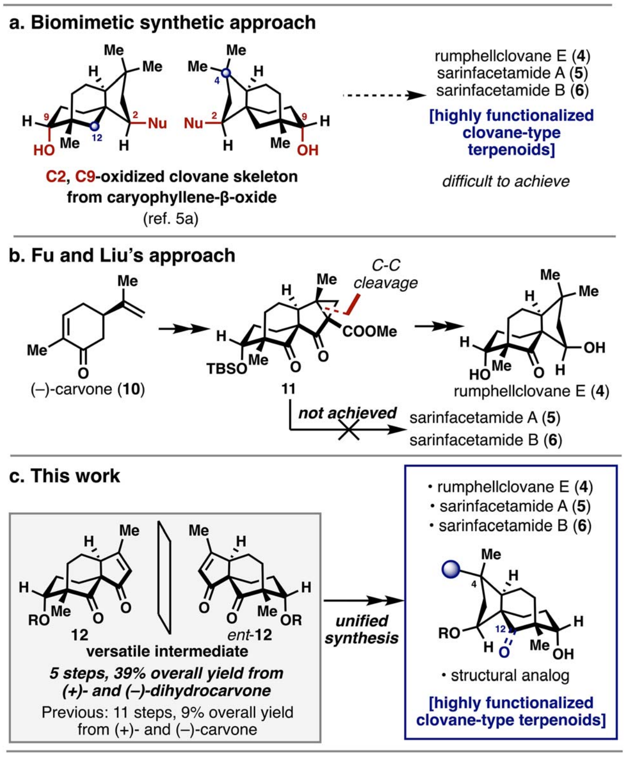


Fig. 2 Reported synthetic efforts of highly functionalized clovane-type terpenoids and this work.

A retrosynthetic analysis of the target clovanes is outlined in Fig. 3. In principle, these highly functionalized clovane-type terpenoids could be accessed divergently from an enantiomer of a versatile intermediate (**12**). We hypothesized that rumphellclovane E (**4**) would be prepared from **12** *via* conjugate addition of a methyl nucleophile and regioselective and diastereoselective reduction of the C2 ketone carbonyl group. We assumed that sarinfacetamides A (**5**) and B (**6**) would be prepared from acetamide **13** by elongation of the C4 side chain moiety. We envisioned that a vinyl group would serve as a precursor to the C4 side chain structure. Acetamide **13**, in turn, would be synthesized from the enantiomer of **12** (*ent*-**12**) by conjugate addition of a vinyl nucleophile, nitrogen atom incorporation, and deoxygenation. Reflecting on our previous synthesis, we sought to drastically shorten the route to the versatile intermediates (**12**/*ent*-**12**). In the previous synthesis,[8] the construction of the tricyclo[6.3.1.0^{1,5}]dodecane core of the clovane skeleton relied on eight steps and multiple transformations, and the introduction of the C2 oxygen functionality required three steps. We envisioned that the cyclopentenone moiety of **12**/*ent*-**12** could be constructed from aldehyde **14**/*ent*-**14**, with the bicyclo[3.3.1]nonane motif of **15** assembled through the domino Michael–aldol reaction[9] of β-ketoaldehyde **17**/*ent*-**17** and acrolein (**15**) in a single step. Although the construction of bicyclo[3.3.1]nonane motifs *via* Michael–aldol sequences is well-established, its applications in terpenoid synthesis are limited,[10] and there is scant precedent for controlling the stereoselectivity of the aldol step.

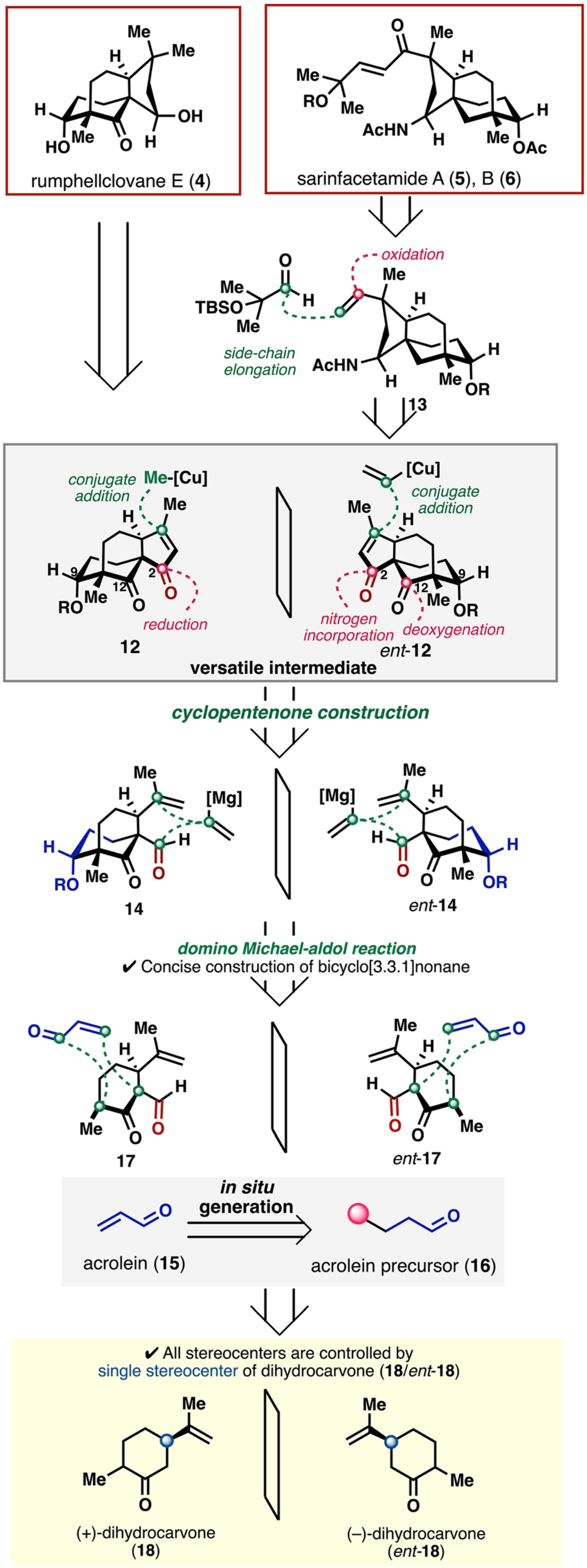
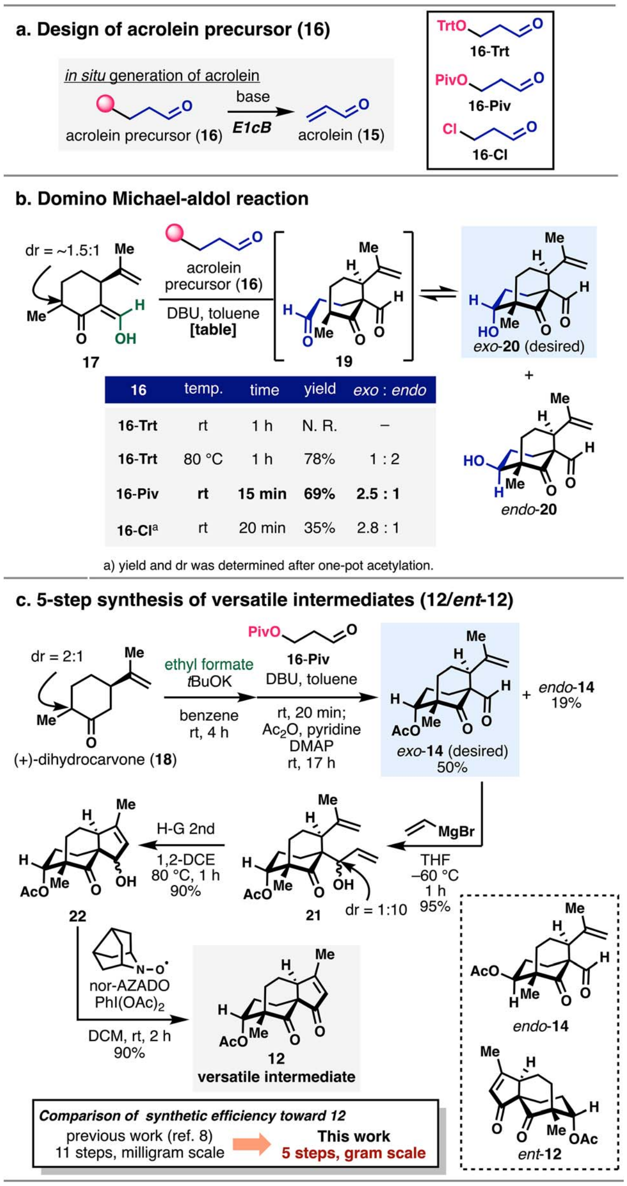


Fig. 3 Retrosynthetic analysis of rumphellclovane E (**4**) and sarinfacetamides A (**5**) and B (**6**).

More importantly, as of 2025, there are limited reliable and practical suppliers of reagent-grade acrolein, mainly due to its instability and toxicity. This situation prompted us to develop a novel methodology to generate acrolein from an appropriate precursor (**16**) *in situ*. β-Ketoaldehyde **17**/*ent*-**17** can be readily derived from dihydrocarvone (**18**/*ent*-**18**) through a conventional formylation.[11] In this revised plan, the C2 oxygen functional group of the versatile intermediate is introduced early in the synthesis as an activating group (formyl group in **17**/*ent*-**17**) for the domino Michael–aldol reaction, rationally avoiding late-stage functional group manipulations. Importantly, all stereocenters on the clovane skeleton can be controlled by the single stereocenter of (+)- or (−)-dihydrocarvone (**18**/*ent*-**18**).

Results and discussion

Based on the revised retrosynthesis, we initiated our investigation by examining the domino Michael–aldol reaction using an acrolein precursor (Scheme 1a). Krische *et al.* generated acrolein as a transient intermediate by employing the logic of hydrogen atom transfer for a substrate with allylic alcohols or monoprotected 1,3-propanediol.[12] Since acrolein is employed as an electrophile to undergo 1,2-addition of allyl iridium species in their studies, it doesn't seem easy to use generated acrolein as a Michael acceptor. To solve this problem, we focused on easy-to-handle acrolein precursors such as **16**, a propanal bearing a leaving group (trityloxy, **16-Trt**, pivaloyloxy, **16-Piv**, or chloride, **16-Cl**) at the β-position. These precursors can release acrolein (**15**) through E1cB elimination in the presence of a base. Released acrolein can participate in the subsequent reaction without purification. These features are convenient for our



16	temp.	time	yield	*exo* : *endo*
16-Trt	rt	1 h	N. R.	–
16-Trt	80 °C	1 h	78%	1 : 2
16-Piv	**rt**	**15 min**	**69%**	**2.5 : 1**
16-Cl[a]	rt	20 min	35%	2.8 : 1

a) yield and dr was determined after one-pot acetylation.

Scheme 1 Synthesis of a versatile intermediate (**12**).

intended domino Michael–aldol sequence because the reaction is typically conducted under basic conditions.

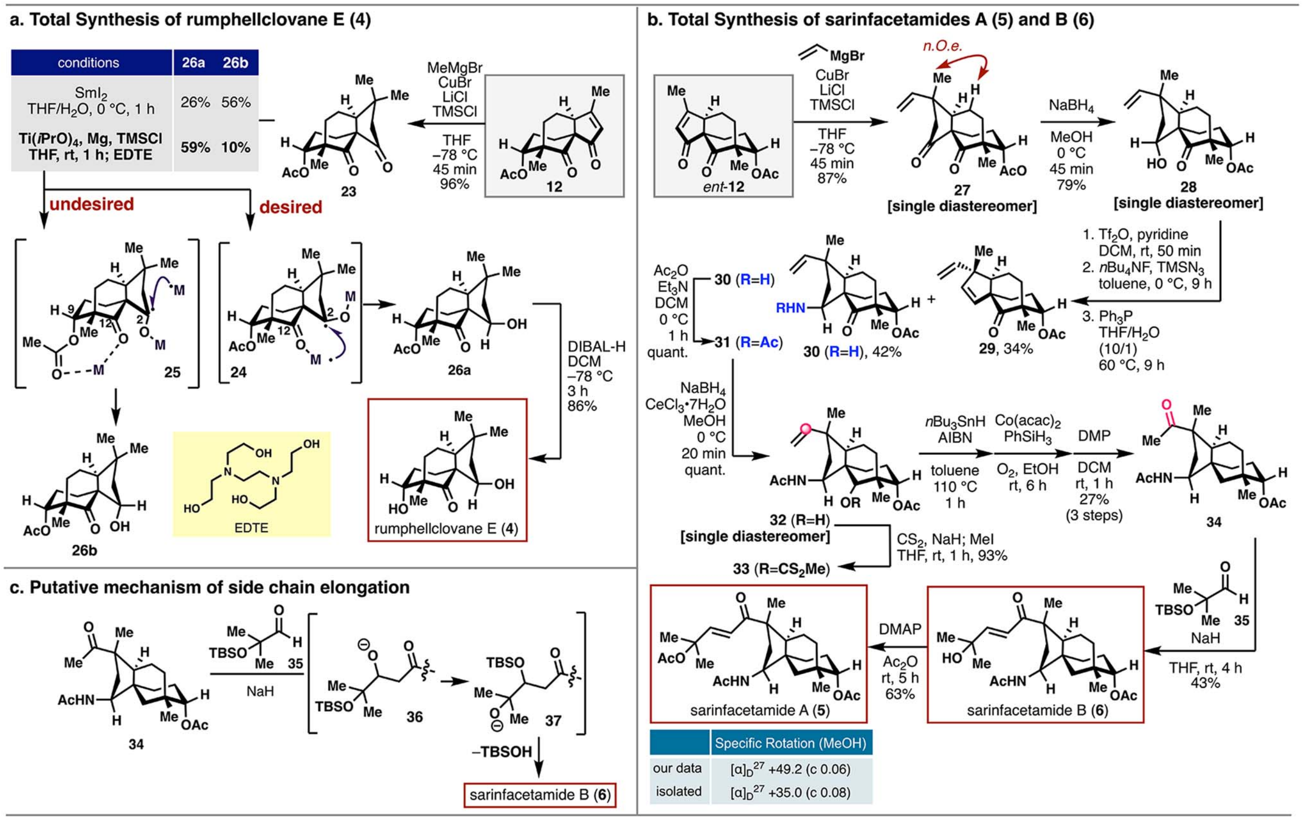
Following this strategy, we initiated the optimization of the domino Michael–aldol reaction using β-ketoaldehyde **17** derived from (+)-dihydrocarvone (**18**) *via* formylation (Scheme 1b). **17** was synthesized as a mixture of diastereomers, and during the synthesis, the diastereomeric ratio changed with subtle variations under the reaction conditions. While **16-Trt** failed to release acrolein at room temperature in the presence of DBU, increasing the temperature led to the slow disappearance of **16-Trt** and the generation of the desired cyclized product **20**.

After the reaction, **20** was obtained as an inseparable mixture of diastereomers, with undesired *endo*-**20** being the main diastereomer (78%, *exo* : *endo* = 1 : 2). The definition of *exo*/*endo* is based on the stereochemistry of the newly generated hydroxy group at C9. This result is presumably owing to its thermodynamic stability. Heating the mixture of *endo*-**20** and *exo*-**20** in the presence of a base further increased the proportion of *endo*-**20**, confirming its thermodynamically favored character (see the SI for details). Reasoning that the desired *exo* isomer would be kinetically favored, we sought milder conditions to reverse the stereoselectivity. Specifically, we anticipated that changing the leaving group from an alkoxy to an acyloxy group, which has a higher leaving ability than the alkoxy group, would achieve this goal. As expected, **16-Piv** released acrolein at room temperature,[13] favoring the formation of the desired *exo* isomer (69%, *exo* : *endo* = 2.5 : 1). The same conditions were also applied to **16-Cl**, which has a higher leaving ability, and the results were evaluated after one-pot acetylation. Compared with **16-Piv**, the yield was significantly lower with similar diastereoselectivity (35%, *exo* : *endo* = 2.8 : 1).

Based on this successful domino Michael–aldol reaction, we focused on a concise synthesis of the versatile intermediate (**12**) (Scheme 1c). After the domino Michael–aldol reaction, the resulting alcohol **20** was acetylated in a one-pot procedure using Ac_2O, pyridine, and DMAP to afford aldehyde **14**. At this point, *exo*-**14** and *endo*-**14** were easily separated by silica gel column chromatography, and we obtained the desired *exo*-**14** in 50% yield. Although we had employed a TBS group to protect the C9 hydroxyl group in our previous synthesis,[8] in alcohol **20**, TBS protection was accompanied by side reactions involving the formyl group or epimerization *via* a retro-aldol reaction. As sarinfacetamides possess an acetoxy group at C9, we opted to use an acetyl group for protection despite concerns about its potential instability. The cyclopentene ring was then rapidly constructed by 1,2-addition of vinylmagnesium bromide (*exo*-**14** to **21**), followed by ring-closing metathesis[14] to obtain allylic alcohol **22** as a mixture of diastereomers. Finally, nor-AZADO[15]-catalyzed oxidation of **22** furnished the desired versatile intermediate (**12**). This synthesis of **12** represents a significant improvement in efficiency and conciseness compared to our previous work[8] (eleven steps *vs.* five steps). The (−)-enantiomer of the versatile intermediate (*ent*-**12**) from (−)-dihydrocarvone (*ent*-**18**) was synthesized using the same route. The efficiency of this synthesis enabled the preparation of both enantiomers of the versatile intermediate on a multigram scale (see the SI for details).

With a robust and efficient route to **12** established, we focused on synthesizing rumphellclovane E (**4**) (Scheme 2a). 1,4-Addition of a Gilman reagent to **12** efficiently provided diketone **23** bearing the desired dimethyl cyclopentanone moiety. Subsequent diastereoselective reduction of **23** was then examined. Fu and Liu reported that SmI_2 imparted the desired diastereoselectivity on substrates similar to **23** in their total synthesis of rumphellclovane E.[7] Unexpectedly, in the case of diketone **23**, the undesired **26b** was the major product. According to their proposed mechanism, the C12 ketone carbonyl directs the selective single-electron transfer from the β-plane of the C2 ketone carbonyl group (see intermediate **24**).

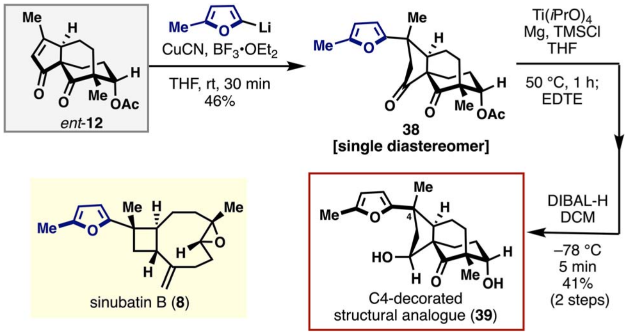
We hypothesized that, owing to the relatively large ionic radius of samarium,[16] bidentate coordination to Sm(II) occurs through the C12 ketone carbonyl and the C9 acetoxy group (see intermediate **25**). This coordination would favor reduction from



Scheme 2 Total synthesis of rumphellclovane E (4) and sarinfacetamides A (5) and B (6).

the more vacant α-face, leading to the preferential formation of **26b**. To circumvent this undesired coordination, we explored metallic single-electron reductants with smaller ionic radii than samarium. We ultimately found that a low-valent titanium reagent,[17] possessing a smaller ionic radius and strong oxygen affinity, effectively promoted the diastereoselective reduction to furnish alcohol **26a**. Treatment with EDTE (*N*,*N*,*N*′,*N*′-tetrakis(2-hydroxyethyl)-ethylenediamine) proved crucial to prevent undesired aggregation of the titanium reagent and enable efficient recovery of **26a**.[18] Finally, deprotection of the acetyl group with DIBAL-H completed the enantioselective total synthesis of rumphellclovane E (**4**). The spectral data of our synthetic sample matched those reported by Fu and Liu (see the SI for details).

Encouraged by this success, we focused on synthesizing sarinfacetamides A (**5**) and B (**6**) (Scheme 2b). The introduction of a vinyl group as a side chain precursor to *ent*-**12** was accomplished diastereoselectively *via* conjugate addition of an organocuprate reagent, affording diketone **27**. Treatment of **27** with NaBH4 allowed a regio- and stereoselective reduction of the C2 ketone carbonyl group smoothly providing β-alcohol **28** as a single diastereomer. We then attempted to incorporate the acetamide moiety into β-alcohol **28** *via* a stereochemical inversion manner. Direct incorporation of an amine or acetamide functional group (*via* Mitsunobu or Ritter-type reaction; see the SI for details) proved challenging, primarily owing to the elimination of the C2 functional group to form alkene **29**. Therefore, we opted to use azide as a nucleophile. A combination of $TMSN_3$ and TBAF[19] proved optimal for azide introduction. Although we could not completely suppress the undesired elimination, we obtained the amine **30** after the Staudinger reduction of the azide compound. We then obtained the desired acetamide **31** by acetylation of **30**. Subsequent removal of the sterically hindered C12 ketone oxygen was achieved through a three-step reaction sequence: Luche reduction[20] to obtain alcohol **32**, xanthate (**33**) synthesis, and Barton–McCombie deoxygenation. Then, we proceeded to the final task, namely, elaborating the side chain. We accomplished this transformation by utilizing Mukaiyama hydration and following Dess–Martin oxidation to give methylketone **34**. Obtained methylketone **34** was condensed with aldehyde **35** (ref. 21) using NaH as a base. Fortunately, this condition promoted not only the aldol condensation but also concomitant deprotection of the TBS group, presumably *via* 1,2-silyl migration of aldolate **36** and the following E1cB elimination of the TBS-oxy group (see intermediate **37**) to furnish sarinfacetamide B (**6**) (Scheme 2c). The first total synthesis of sarinfacetamide A (**5**) was then achieved by acetylation of sarinfacetamide B (**6**) using DMAP in a solvent amount of Ac_2O. Presumably, owing to the steric hindrance of the tertiary alcohol, standard acetylation conditions (Ac_2O/Et_3N/DMAP) were ineffective. All the spectral data of our synthetic samples of sarinfacetamides A (**5**) and B (**6**) were in agreement with those reported for the isolated natural products. Furthermore, the specific rotations of our synthetic samples matched those of the natural products (see the SI for details).



Scheme 3 Synthesis of a C4-decorated structural analogue (**39**).

The successful total synthesis of the sarinfacetamides highlights the versatility of our versatile intermediate (**12**/*ent*-**12**). However, as discussed above, the presence of xeniaphyllane-type terpenoids bearing diverse substituents at the C4 position, along with the potential for their biosynthetic rearrangement into clovane-type skeletons (Fig. 1b), suggests the existence of unexplored structural diversity among C4-decorated clovanes. Our versatile intermediate (**12**/*ent*-**12**) offers a platform to address this possibility: nucleophilic addition to the enone moiety enables access to a variety of C4-decorated clovane-type skeletons. Motivated by this prospect, we pursued the synthesis of a C4-decorated structural analogue. However, modifications to the enone moiety of **12**/*ent*-**12** have been limited to relatively small nucleophiles, such as methyl and vinyl groups. This prompted us to ask: is it possible to introduce a bulkier nucleophile into C4 and construct an all-carbon quaternary chiral center? This question sparked our curiosity.

As a test case, we selected a 5-methylfuranyl cuprate (Scheme 3). Notably, sinubatin B (**8**), a member of the xeniaphyllane family, features a similar substitution pattern at the C4 position. We began the synthesis of C4-decorated structural analogue **39** by introducing a furan moiety to *ent*-**12**. Conjugate addition of a furan nucleophile to obtain **38** was achieved, albeit in moderate yield, using a higher-order cuprate reagent reported by Lipshutz.[22] Note that standard conjugate addition conditions were not effective, presumably due to the steric hindrance of the enone moiety. Subsequent stereoselective reduction was accomplished with a low-valent titanium reagent, as in the synthesis of rumphellclovane E (**4**). Finally, deprotection of the acetyl group with DIBAL-H completed the synthesis of **39**.

Conclusions

The collective total synthesis of the highly functionalized clovane-type terpenoids rumphellclovane E (**4**) and sarinfacetamides A (**5**) and B (**6**) was achieved *via* versatile intermediates **12**/*ent*-**12**, prepared from (+)- or (−)-dihydrocarvone (**18**/*ent*-**18**, respectively). Enantiocontrolled access to the ideally functionalized clovane-type skeleton of **12** was accomplished in five steps, enabled by a key domino Michael–aldol reaction employing acrolein surrogate **16-Piv** under basic conditions. Inspired by sinubatin B (**8**), we further synthesized a structural analogue (**39**) by conjugate addition of a furan nucleophile to the enone moiety of a versatile intermediate (*ent*-**12**), followed by a two-step transformation. It should be noted that the versatile intermediate **12**/*ent*-**12** provides access to the diversification at the C4 position of the clovane skeleton, which has been suggested to have unknown structural diversity. Therefore, our strategy, based on both enantiomers of **12**/*ent*-**12**, should enable both unified and divergent access to currently known functionalized clovane-type terpenoids and a structural analogue. The first demonstration of the wide versatility of our designed intermediate **12**/*ent*-**12** would lead to further studies of this type of terpenoid, including biological studies.

Author contributions

S. N. and Y. I. conceived the project. D. N. carried out the synthetic work and data collection. D. N. and S. N. prepared the draft of the manuscript. All authors contributed to the discussion of the results and the revision of the manuscript.

Conflicts of interest

There are no conflicts of interest to declare.

Data availability

The experimental data supporting this article, including procedure and spectrum have been included as part of the SI.

Supplementary information is available. See DOI: https://doi.org/10.1039/d5sc04197j.

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Notes and references

1 (*a*) J. Tamiya and E. J. Sorensen, *J. Am. Chem. Soc.*, 2000, **122**, 9556–9557; (*b*) F. Le Bideau, M. Kousara, L. Chen, L. Wei and F. Dumas, *Chem. Rev.*, 2017, **117**, 6110–6159; (*c*) R. Matsuo, A. Watanabe, S. Kamo, A. Matsuzawa and K. Sugita, *Org. Chem. Front.*, 2021, **8**, 6063–6066; (*d*) Y. Xue and G. Dong, *J. Am. Chem. Soc.*, 2021, **143**, 8272–8277; (*e*) Z. Wang, Z. Song, J. Huang and Z. Yang, *J. Am. Chem. Soc.*, 2024, **146**, 4363–4368.

2 (*a*) Y. Fukuyama, Y. Otoshi, M. Kodama, T. Hasegawa and H. Okazaki, *Tetrahedron Lett.*, 1990, **31**, 4477–4480; (*b*) Y. Fukuyama, Y. Otoshi, K. Miyoshi, K. Nakamura, M. Kodama, M. Nagasawa, T. Hasegawa, H. Okazaki and

M. Sugawara, *Tetrahedron*, 1992, **48**, 377–392; (*c*) W.-Y. Tsui and G. D. Brown, *J. Nat. Prod.*, 1996, **59**, 1084–1086; (*d*) H.-M. Chung, Y.-H. Chen, T.-L. Hwang, L.-F. Chuang, W.-H. Wang and P.-J. Sung, *Tetrahedron Lett.*, 2010, **51**, 2734–2736; (*e*) H.-M. Chung, T.-L. Hwang, Y.-H. Chen, J.-H. Su, M.-C. Lu, J.-J. Chen, J.-J. Li, L.-S. Fang, W.-H. Wang and P.-J. Sung, *BCSJ*, 2011, **84**, 119–121; (*f*) H.-M. Chung, W.-H. Wang, T.-L. Hwang, Y.-C. Wu and P.-J. Sung, *Nat. Prod. Commun.*, 2013, **8**, 1037–1040; (*g*) H.-M. Chung, J.-H. Su, T.-L. Hwang, J.-J. Li, J.-J. Chen, Y.-H. Chen, Y.-C. Chang, Y.-D. Su, Y.-H. Chen, L.-S. Fang, J.-H. Sheu, W.-H. Wang and P.-J. Sung, *Tetrahedron*, 2013, **69**, 2740–2744; (*h*) F.-W. Dong, Y. Liu, Z.-K. Wu, W. Gao, C.-T. Zi, Y. Dan, H.-R. Luo, Z. Jun and J.-M. Hu, *Fitoterapia*, 2015, **102**, 27–34; (*i*) A. M. White, G. K. Pierens, T. Skinner-Adams, K. T. Andrews, P. V. Bernhardt, E. H. Krenske, E. Mollo and M. J. Garson, *J. Nat. Prod.*, 2015, **78**, 1422–1427; (*j*) F. Ye, J. Li, Y. Wu, Z.-D. Zhu, E. Mollo, M. Gavagnin, Y.-C. Gu, W.-L. Zhu, X.-W. Li and Y.-W. Guo, *Org. Lett.*, 2018, **20**, 2637–2640.

3 (*a*) O. Wallach and W. Wallach, *Ann. Chem.*, 1982, **271**, 285–311; (*b*) G. G. Henderson, R. O. O. McCrone and J. M. Robertson, *J. Chem. Soc.*, 1929, 1368–1372; (*c*) L. Fitjer, A. Malich, C. Paschke, S. Kluge, R. Gerke, B. Rissom, J. Weiser and M. Noltemeyer, *J. Am. Chem. Soc.*, 1995, **117**, 9180–9189.

4 (*a*) A. Aebi, D. H. R. Barton and A. S. Lindsey, *J. Chem. Soc.*, 1953, 3124–3129; (*b*) H. Heymann, Y. Tezuka, T. Kikuchi and S. Supriyatna, *Chem. Pharm. Bull.*, 1994, **42**, 138–146; (*c*) I. G. Collado, J. R. Hanson and A. J. Macías-Sánchez, *Tetrahedron*, 1996, **52**, 7961–7972; (*d*) X. Cheng, N. Harzdorf, Z. Khaing, D. Kang, A. M. Camelio, T. Shaw, C. E. Schmidt and D. Siegel, *Org. Biomol. Chem.*, 2012, **10**, 383–393.

5 (*a*) X. Cheng, N. L. Harzdorf, T. Shaw and D. Siegel, *Org. Lett.*, 2010, **12**, 1304–1307; (*b*) J. Yang, W. Xu, Q. Cui, X. Fan, L.-N. Wang and Z.-X. Yu, *Org. Lett.*, 2017, **19**, 6040–6043; (*c*) Y. Zhou, J.-L. Qin, W. Xu and Z.-X. Yu, *Org. Lett.*, 2022, **24**, 5902–5906; (*d*) P. Zhang, J. Eun, M. Elkin, Y. Zhao, R. L. Cantrell and T. R. Newhouse, *Nat. Synth.*, 2023, **2**, 527–534; (*e*) T. Suzuki, K. Yamashita, W. Ikeda, K. Ikeuchi and K. Tanino, *Asian J. Org. Chem.*, 2024, **13**, e202400242.

6 (*a*) A. Groweiss and Y. Kashman, *Tetrahedron Lett.*, 1978, 2205–2208; (*b*) A. F. Ahmed, J.-H. Su, R.-T. Shiue, X.-J. Pan, C.-F. Dai, Y.-H. Kuo and J.-H. Sheu, *J. Nat. Prod.*, 2004, **67**, 592–597; (*c*) S.-P. Chen, A. F. Ahmed, C.-F. Dai, C.-K. Lu, W.-P. Hu, J.-J. Wang and J.-H. Sheu, *Tetrahedron*, 2006, **62**, 6802–6807; (*d*) S.-P. Chen, J.-H. Su, A. F. Ahmed, C.-F. Dai, Y.-C. Wu and J.-H. Sheu, *Chem. Pharm. Bull.*, 2007, **55**, 1471–1475; (*e*) S.-P. Chen, J.-H. Su, H.-C. Yeh, A. F. Ahmed, C.-F. Dai, Y.-C. Wu and J.-H. Sheu, *Chem. Pharm. Bull.*, 2009, **57**, 162–166; (*f*) F.-Y. Hsu, S.-K. Wang and C.-Y. Duh, *Mar. Drugs*, 2018, **16**, 40; (*g*) Z.-H. Chen, S.-Q. Lu, G.-Y. Han, X.-W. Li and Y.-W. Guo, *Mar. Drugs*, 2022, **20**, 272.

7 G. Liu, Z. Zhang, S. Fu and B. Liu, *Org. Lett.*, 2021, **23**, 290–295.

8 D. Ninomiya, S. Nagasawa and Y. Iwabuchi, *Org. Lett.*, 2022, **24**, 7572–7576.

9 M. Ruiz, P. López-Alvarado, G. Giorgi and J. C. Menéndez, *Chem. Soc. Rev.*, 2011, **40**, 3445.

10 (*a*) K. C. Nicolaou, G. E. A. Carenzi and V. Jeso, *Angew. Chem., Int. Ed.*, 2005, **44**, 3895–3899; (*b*) Y. Xia and A. P. Kozikowski, *J. Am. Chem. Soc.*, 1989, **111**, 4116–4117; (*c*) E. J. Corey and S. Nozoe, *J. Am. Chem. Soc.*, 1963, **85**, 3527–3528.

11 H. H. Elghandour, R. Faure, A. Frideling, J.-P. Galy, I. Alkorta and J. Elguero, *Heterocycles*, 2002, **57**, 307.

12 (*a*) C. C. Meyer, K. L. Verboom, M. M. Evarts, W.-O. Jung and M. J. Krische, *J. Am. Chem. Soc.*, 2023, **145**, 8242–8247; (*b*) K. L. Verboom, C. C. Meyer, M. M. Evarts, W.-O. Jung and M. J. Krische, *Org. Lett.*, 2023, **25**, 3659–3663.

13 Further investigation of the utility of **16-Piv** as an equivalent of acrolein is undergoing, and it will be reported in due course.

14 We also examined the Prins reaction of aldehyde **14**. Although the reaction proceeded under various Lewis acidic conditions, only a mixture of alkene regioisomers was obtained. However, the isomerization of alkenes following the oxidation of alcohols was difficult, probably due to the steric factors of the substrates.

15 M. Hayashi, Y. Sasano, S. Nagasawa, M. Shibuya and Y. Iwabuchi, *Chem. Pharm. Bull.*, 2011, **59**, 1570–1573.

16 R. D. Shannon, *Acta Crystallogr., Sect. A*, 1976, **32**, 751–767.

17 S. Okamoto, *Chem. Rec.*, 2016, **16**, 857–872.

18 J. T. Reeves, Z. Tan, Z. S. Han, G. Li, Y. Zhang, Y. Xu, D. C. Reeves, N. C. Gonnella, S. Ma, H. Lee, B. Z. Lu and C. H. Senanayake, *Angew. Chem., Int. Ed.*, 2012, **51**, 1400–1404.

19 (*a*) E. D. Soli, A. S. Manoso, M. C. Patterson, P. DeShong, D. A. Favor, R. Hirschmann and A. B. Smith, *J. Org. Chem.*, 1999, **64**, 3171–3177; (*b*) B. Sameem, P. Karuso and F. Liu, *Tetrahedron Lett.*, 2022, **113**, 154245.

20 A single diastereomer was obtained in this Luche reduction (see the SI for details). However, the stereocenter was removed in the subsequent Barton–McCombie deoxygenation, and thus its stereochemistry was not determined.

21 M. S. Ahmed, L. C. Kopel and F. T. Halaweish, *ChemMedChem*, 2014, **9**, 1361–1367.

22 J. S. Ng, J. R. Behling, A. L. Campbell, G. D. Searle, D. Nguyen and B. Lipshutz, *Tetrahedron Lett.*, 1988, **29**, 3045–3048.