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First stereoselective approach for structure revision of nagiol and syntheses of 2,3-dihydroxyferruginol and ferruginol†

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We report the first enantioselective total synthesis of nagiol, accompanied by a revision of its previously proposed structure. This synthetic strategy has been successfully extended to the total synthesis of (+)-ferruginol as well as to the 2,3-dihydroxyferruginol. Enantiomerically enriched 8,11,13-podocarpa-triene-3-ol was utilized as a versatile and efficient precursor to access the abietane diterpenoid frame-work. Functionalization of the aromatic C-ring on podocarpatriene was achieved through regioselective Friedel−Crafts acylation and further modification. Two distinct strategies were employed to install the 2,3-dihydroxy functionality on the A-ring: (i) selective elimination followed by *syn*-stereoselective dihydroxyla-tion, and (ii) α-oxygenation of the ketone followed by highly diastereoselective reduction of the diketone intermediates. These methods allowed access to possible C-2/C-3 *syn*-isomers for comparative spectro-scopic analysis. Careful comparison of the NMR data of the synthetic products with the reported values, in conjunction with single-crystal X-ray diffraction studies, led to a revision of the originally proposed structure of nagiol. Furthermore, this study presents the first enantioselective synthesis of 2,3-dihydroxy-ferruginol, revealing certain structural discrepancies among the isolation reports.

Introduction

Aromatic abietane diterpenoids are widely distributed through-out the plant kingdom and are well recognized for their diverse biological activities.[1–7] Remarkably, certain abietane-type diterpenoids exhibit significant stability, having been iso-lated from geological samples such as fossils, sediments, coals, and petroleum deposits in non-decomposed form.[8] These compounds play important roles in everyday life, serving as food additives, perfuming agents, and pharmaco-logical agents. Biogenetically, aromatic abietanes are typically derived from a cationic polycyclization of geranylgeranyl pyro-phosphate (GGPP), initially forming miltiradienes that undergo oxidative aromatization to yield C-ring aromatic abietanes.[9–11] Subsequent enzymatic oxidations at various carbon atoms within the tricyclic ring system further diversify these structures, resulting in a broad range of derivatives (Fig. 1). Nagiol (2), an abietane mono—norditerpenoid, was isolated as a white amorphous powder from the leaves of *Podocarpus nagi* by a Chinese research group in 2017.[12]

Spectroscopic analyses, including NMR, UV, IR, and mass spectrometry, revealed that compound **2** is a tricyclic norditer-penoid bearing a C-15 ketone functionality and three hydroxyl groups, one of which is a phenolic moiety. Structural elucida-tion further indicated that in compound **2**, an acetyl group replaces the isopropyl substituent found in ferruginol (**3**), accompanied by oxidation at the C-2 and C-3 positions. The relative configuration at C-2 and C-3 in compound **2** was estab-lished through analysis of NMR coupling constants, ROESY correlations, and biogenetic considerations.
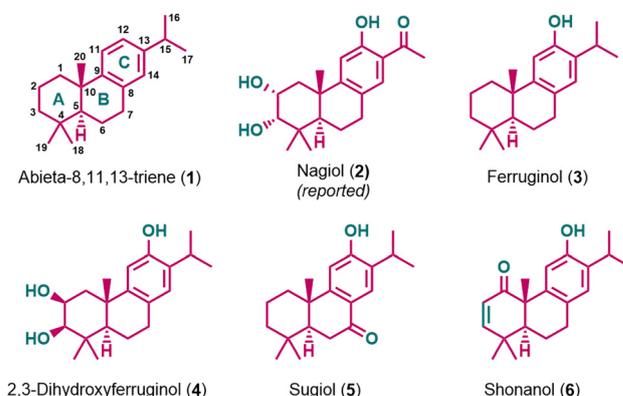

Fig. 1 Natural aromatic abietane diterpenoids.

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The parent compound ferruginol (3) is one of the most extensively studied members of the abietane class of diterpenoids. It was first isolated in 1939 from *Podocarpus ferrugineus* by Brandt and Neubauer.[13] Since then, numerous research groups have reported its isolation from a wide range of plant species distributed across the globe.[14–18] Notably, ferruginol exhibits a broad spectrum of biological activities, including cardioprotective,[14] gastroprotective,[19–21] antitumour,[22,23] antimalarial,[24,25] anti-inflammatory,[26] anti-SARS[27,28] and several other pharmacological effects.[6,14,29] The structural diversification of ferruginol in biological systems through site-selective oxidations has led to the discovery of several analogues with oxygenated functionalities at key positions. For example, the 2,3-dihydroxy-substituted analogue (4) was first identified in 2007 by GC-MS analysis in various members of the Cupressaceae family, including the shoots of *Athrotaxis laxifolia* and *Athrotaxis selaginoides*.[30] Later, in 2017, Chen and co-workers isolated compound 4 along with nagiol (2) from *Podocarpus nagi*.[12] More recently, in 2022, Liang and co-workers reported the isolation of compound 4 from the aerial parts of *Gaultheria leucocarpa* var. *yunnanensis*, alongside several other abietane-type diterpenoids.[31]

We recently synthesized the possible stereoisomers of isolophanthin E to establish its correct structure, with the support of extensive NMR spectroscopic analysis.[32] During this investigation, we undertook a comprehensive analysis of the chemical shift trends in abietane-type diterpenoids featuring a 2,3-dihydroxy substitution pattern on the A-ring. It was observed that the C-2/C-3 *anti*-isomers typically display relatively upfield chemical shifts (δ < 4.0 ppm for H-2 and δ < 3.0 ppm for H-3), whereas the corresponding *syn*-isomers exhibit downfield shifts (δ > 4.0 ppm for H-2 and δ > 3.2 ppm for H-3).
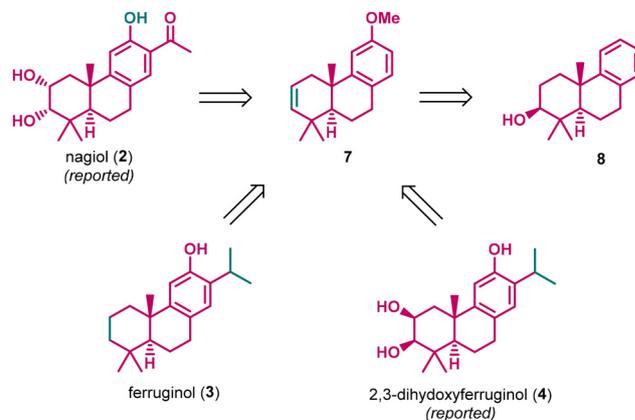
In the originally reported structure of nagiol, the chemical shifts at δ 4.23 ppm for H-2 and δ 3.23 ppm for H-3 were interpreted to support a C-2α/C-3α *syn*-configuration.[12] However, during our studies on the synthesis of isolophanthin E, we observed significant differences in their NMR characteristics; the reported data of nagiol more closely resembled those of the C-2β/C-3β *syn*-isomer of isolophanthin E synthesized in our laboratory. In particular, the H-3 proton resonance at δ 3.23 ppm is more consistent with an axial orientation. This apparent discrepancy in the assignment of relative configuration prompted us to undertake the total synthesis of nagiol. Moreover, the total synthesis of nagiol has not been reported in the literature. Additionally, the synthetic route developed for nagiol could potentially enable access to structurally related natural products such as 2,3-dihydroxyferruginol (4) and ferruginol (3), further expanding the scope of this abietane-derived chemical space.

Herein, we report an enantioselective synthetic approach to nagiol (2), 2,3-dihydroxyferruginol (4), and ferruginol (3), starting from an enantiomerically pure synthetic 3-hydroxy-podocarpa-8,11,13-triene. To install the 2,3-dihydroxy functionality on the A-ring of nagiol (2), two distinct strategies were developed: (i) elimination of the hydroxyl group followed by *syn*-selective dihydroxylation, and (ii) α-oxygenation of a ketone fol-

lowed by stereoselective reduction of the resulting α-diketone. Several synthetic routes to ferruginol (3) have been previously developed, including strategies from relatively abundant diterpenoid precursors, and most of these utilize racemic materials.[33] The first total synthesis was reported in 1942 from podocarpic acid.[34] Subsequently, the Oishi group utilized dehydroabietic acid,[35] while the Marcos[36] and Álvarez-Manzaneda[37] groups independently developed routes starting from sclareol. González and co-workers employed dehydroabietamine as a starting material.[38] In addition, numerous stereoselective approaches have been developed for the synthesis of (+)- and (−)-ferruginol.[33] Among the various strategies explored, cationic polyene cyclization has emerged as a powerful tool for constructing the tricyclic core of ferruginol.[39,40] Our study presents a new enantioselective route to (+)-ferruginol using synthetic (+)-podocarpatriene-3-ol as the starting material, offering a concise and stereocontrolled access to this important class of abietane diterpenoid.

Results and discussion

The retrosynthetic analysis for our primary target molecule, nagiol (2), is outlined in Scheme 1. We envisioned that the core structure of nagiol (2) could be constructed through a sequence of strategic transformations, starting from a suitably functionalized podocarpatriene-3-ol 8. Key to our strategy was the formation of the advanced intermediate 7, which could be accessed from 8 *via* regioselective Friedel–Crafts acylation, followed by Baeyer–Villiger oxidation and dehydration to introduce the olefinic moiety and install the required oxygen functionality. Intermediate 7 would then serve as a versatile branching point; through asymmetric dihydroxylation and further elaboration, it would furnish compound 2. Similarly, 2,3-dihydroxyferruginol (4) was expected to be obtained from compound 7 *via* selective dihydroxylation followed by functional group modification. Additionally, ferruginol (3) could be accessed from intermediate 7 *via* olefin reduction and isopropyl group installation.


Scheme 1 Retrosynthetic analysis of nagiol (2), ferruginol (3), and 2,3-dihydroxyferruginol (4).
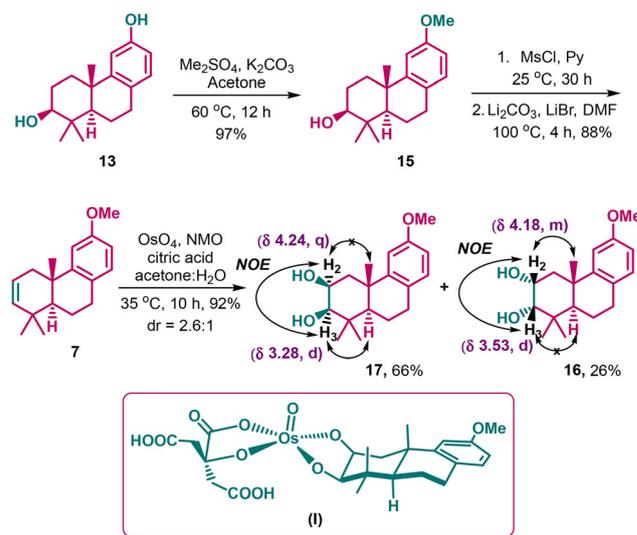
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We initiated our synthesis from the tricyclic compound podocarpatriene-3-ol (**8**) prepared on a gram scale in our lab.[41] Synthesis of **8** is well documented by several groups using cationic polyenecyclization.[42–45] We prepared **8** from enantiomerically pure epoxy geranyl acetate[46] for this study. To install a C-12 hydroxy group in **8**, we employed a regioselective Friedel–Crafts acylation followed by Baeyer–Villiger oxidation and methanolysis reactions (Scheme 2). The Friedel–Crafts reaction of compound **8** resulted in an inseparable mixture of regioisomers, specifically the C-12 and C-13 acylated products (**9** and **10**), in a ratio of 4 : 1 in 90% yield. The formation of the desired isomer in the major amount was further confirmed through NOESY studies. Though the podocarpatriene-3-ol **8** is well known, our approach marks the first report of the regioselective Friedel–Crafts reaction on its aromatic ring. The combined mixture of regioisomers (**9** and **10**) was then treated with *meta*-chloroperbenzoic acid to form the corresponding rearranged acetates **11** and **12**. The mixture when subjected for Fries rearrangement reactions under different catalysts provided complex mixture of products. Hence, we proceeded with crude mixture for direct methanolysis in the presence of K$_2$CO$_3$ in methanol to form (2*S*,4a*S*,10a*R*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,6-diol **13** in 69% and (2*S*,4a*S*,10a*R*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,7-diol **14** (isolophanthin C)[47] in 17% isolated yield.

Having the diol **13** on a gram scale in hand, we moved ahead, primarily with the selective protection of the phenolic hydroxy group. Methylation using dimethyl sulfate and potassium carbonate produced compound **15** in 97% yield. Further, the secondary alcohol in **15** was subjected to mesylation, followed by elimination in the presence of Li$_2$CO$_3$ and LiBr, heating at 100 °C in DMF to afford the olefin **7**. Then, compound **7** underwent citric acid-assisted OsO$_4$-catalyzed *syn*-dihydroxylation,[48] forming *syn*-

diols **16** and **17** in a 1 : 2.6 ratio in 92% yield.[49] It was expected that the *exo*-addition proceeds through (**I**) as it prefers the less hindered convex outer face to yield **17** as the major product. Both isomers were separated, and the relative configurations of the two stereogenic centers were confirmed using NOESY data.[50] For compound **16**, NOE correlations of H-2/H-3 suggested that H-2 and H-3 were co-facial, and NOE correlations of Me-19/H-2, Me-20/H-2 confirmed the β-orientation of H-2 and H-3. In case of compound **17**, NOE correlations of H-2/H-3 suggested that both are co-facial, and it shows correlations for Me-18/H-3, H-5/H-3, which confirmed the α-orientation of H-2 and H-3. The required diastereomer, α-diol **16**, was obtained in a yield of 26%. Compound **16** was subjected to Friedel–Crafts acylation, and di-*O*-acetylated and *C*-acylated product **18** was obtained. After acidic workup, the crude was directly subjected to methanolysis in the presence of K$_2$CO$_3$ to get compound **19** as a single regioisomer in 90% yield over two steps. Finally, *O*-methyl deprotection was achieved using boron tribromide, resulting in the formation of the reported structure of nagiol **2** in 96% yield.[51] Spectral data of synthetic **2** were correlated to the reported data of the natural isomer (Scheme 3).[12] Notable differences were found both in ^{1}H and ^{13}C chemical shift values for the C-2, C-3, and C-5 carbon centers.
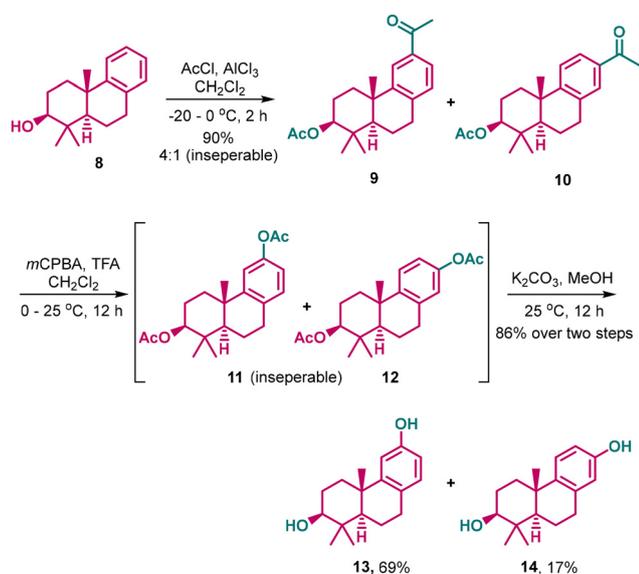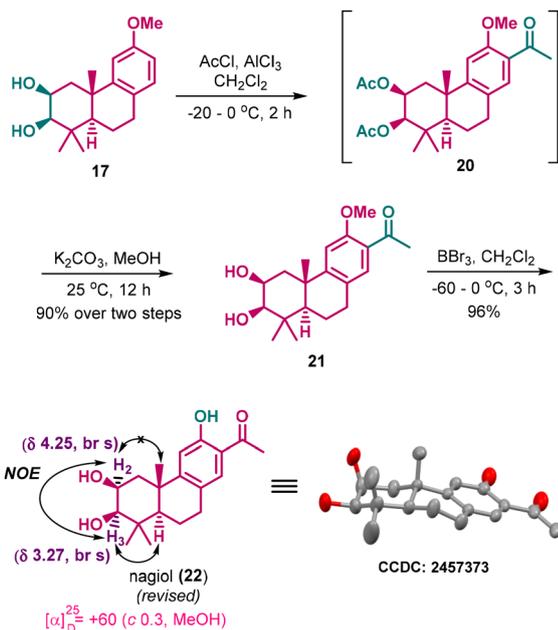

Scheme 2 Regioselective aromatic hydroxylation of podocarpatriene-3-ol (**8**).

Scheme 3 Preparation of the reported structure of nagiol (**2**).

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Scheme 4 Conversion of isomer **17** to nagiol **22**.

Given the structural similarity of compounds **16** and **17** to the target molecule nagiol (**2**), a detailed NMR analysis was undertaken to determine which compound aligned more closely. The proton and carbon chemical shifts at the C-2 and C-3 positions of compound **16** showed a strong correlation with synthetic **2**, indicating that they likely possess the same stereochemistry. In contrast, the NMR shifts for C-2 and C-3 positions of compound **17** were in excellent agreement with the reported values of the natural product.[12] This observation strongly suggests that compound **17** likely shares the same C-2/C-3 stereochemistry as natural nagiol. Accordingly, compound **17** was subjected to a sequence of Friedel–Crafts acylation, methanolysis, and demethylation, which led to the formation of compound **22** (Scheme 4). The NMR data (^{1}H and ^{13}C) of compound **22** showed excellent agreement with the reported values for natural nagiol. Specifically, the proton chemical shifts for H-2 and H-3 were observed at δ 4.25 ppm and δ 3.27 ppm, respectively, while the corresponding carbon signals appeared at δ 71.3 ppm (C-2) and δ 78.1 ppm (C-3), all in close agreement with the spectral data of the natural product (Table 1).[12]

Specific rotation measurements further differentiated the synthetic isomers: synthetic compound **2** showed a specific rotation of $[\alpha]_D^{25}$ +35 (c 0.2, MeOH), while compound **22** exhibited $[\alpha]_D^{25}$ +60 (c 0.3, MeOH), both significantly deviating from the reported value of $[\alpha]_D^{25}$ +6 (c 0.007, MeOH). Despite this discrepancy in specific rotation value, the complete spectral match, especially in NMR data, confirmed that compound **22** is the natural isomer. Thus, its structure was unambiguously established as 1-((4bS,6S,7R,8aR)-3,6,7-trihydroxy-4b,8,8-trimethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthren-2-yl)ethan-1-one, and it was supported by X-ray crystallographic data.

Table 1 Comparison of spectral data of synthetic nagiols with reported data

Carbon number	Natural 2 (reported)[12]		Synthetic 2		Synthetic 22	
	^{1}H NMR^a	^{13}C NMR^b	^{1}H NMR^a	^{13}C NMR^b	^{1}H NMR^a	^{13}C NMR^b
1a	2.70, m	42.3	2.23, m	42.3	2.64, d (1.4)	42.4
1b	1.72, m		1.83, m		1.72, (14.1)	
2a	**4.24, d (3.5)**	**71.2**	**4.18, m**	**66.9**	**4.25, br s**	**71.3**
2b						
3a	**3.27, d (3.5)**	**77.9**	**3.53, s**	**78.6**	**3.27, br s**	**78.1**
3b						
4		38.5		38.5		38.6
5a	1.35, dd (12.4, 2.4)	49.1	1.83, m	39.9	1.36, d (12.0)	49.3
6a	1.90, m	18.6	2.05, m	21.8	1.92, d (7.6)	18.7
6b	1.85, m		2.02, m		1.85, m	
7a	2.95, m	29.6	2.94, m	28.4	2.95, m	29.7
7b	2.80, m		2.83, m		2.81, d (8.6)	
8		125.4		125.8		125.5
9		159.6		158.8		159.7
10		37.8		39.7		38.0
11	6.86, s	113.8	6.87, s	113.5	6.87, s	114.0
12		160.1		160.4		160.3
13		117.9		118.1		118.0
14	7.40, s	131.1	7.40, s	131.1	7.41, s	131.2
15		203.9		204.0		204.0
16	2.57, s	26.3	2.58 s	25.1	2.58, s	26.4
17						
18	1.08, s	29.8	0.98, s	29.2	1.09, s	29.9
19	1.11, s	17.1	1.10, s	18.5	1.11, s	17.2
20	1.43, s	26.5	1.22, s	26.6	1.43, s	26.6
OH-12	11.90, s		11.91, s		11.91, s	
Rotation	$[\alpha]_D^{25}$ +6 (c 0.007, MeOH)		$[\alpha]_D^{25}$ = +35 (c 0.2, MeOH)		$[\alpha]_D^{25}$ = +60 (c 0.3, MeOH)	

^{a} Recorded at 500 MHz. ^{b} Recorded at 126 MHz.

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Having established the structure of nagiol as the C-2β/C-3β *syn*-isomer, we subsequently devised an improved synthetic route starting from the key intermediate **15** (Scheme 5). This revised strategy aimed to achieve enhanced diastereoselectivity and improved yields for the desired *syn*-dihydroxy isomer **17**, thereby streamlining access to the correct stereoisomer of nagiol. We subjected compound **15** to oxidation using Dess–Martin periodinane, which afforded the corresponding keto compound **23** in 98% yield.

Subsequent oxidation of compound **23** using molecular oxygen in the presence of potassium *tert*-butoxide in *tert*-butanol furnished the enol–ketone intermediate **24**.[52,53] This diketone was then directly subjected to stereoselective reduction using NaBH$_4$, delivering the *syn*-diol **17** as the sole product in 87% overall yield over two steps.[52,53] The spectral data and specific rotation are consistent with those of the previously synthesized compound **17**. This highly selective and efficient route enabled a streamlined synthesis of compound **17**, which was subsequently transformed into nagiol (**22**) by following our previously established sequence involving Friedel–Crafts acylation, methanolysis, and demethylation.

Expanding the scope and application of the strategy, 2,3-dihydroxyferruginol (**4**) was readily synthesized from nagiol (**22**). Compound **22** was first subjected to methyl lithium to obtain the corresponding *tert*-alcohol, which was then subjected to hydrogenolysis using Pd/C under a hydrogen atmosphere to afford the reported structure of 2,3-dihydroxyferruginol (**4**), in 92% over two steps (Scheme 6). Both the Simoneit[30] and Liang[31] groups reported the structure of **4** in 2006 and 2022, but neither report provided any spectral data to support the structure. However, when the spectral data of our synthetic compound **4** was compared with the data reported by Chen and co-workers, certain discrepancies were found.[12] To further investigate, we also synthesized the C-2/C-3 *syn*-isomer **25** from synthetic compound **2** using an analogous procedure. Interestingly, the spectral data of compound **25** also deviated from the spectral data reported by Chen and co-workers. Although a racemic synthesis of **4**
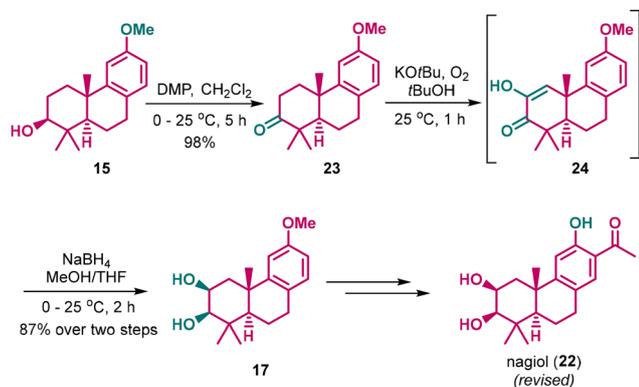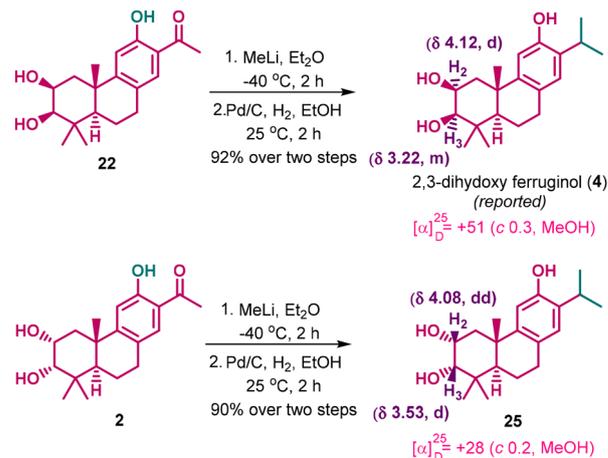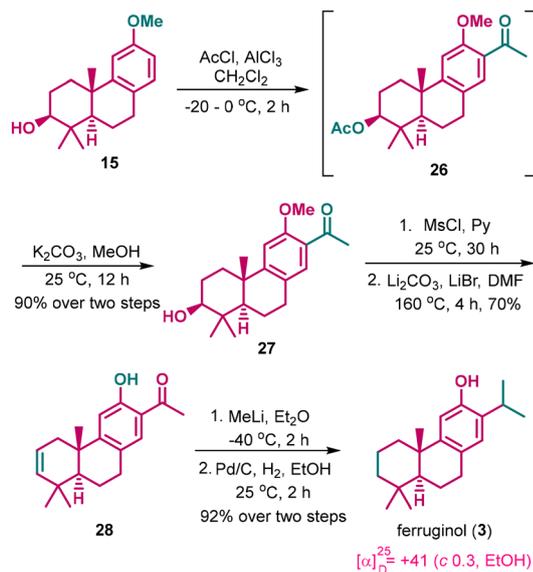

Scheme 6 Synthesis of 2,3-dihydroxyferruginol isomers from nagiol isomers.

and **25** was previously reported by Huo *et al.*,[48] our analysis shows that the spectral data they provided do not match well with the natural product **4** reported by Chen and co-workers.[12] In contrast, the NMR data of our synthetic compounds **4** and **25** are in good agreement with those reported by Huo *et al.*[48] As we do not have any clarity on the spectral data of the first isolation of **4** by Simoneit and co-workers,[30] we conclude that we have synthesized the 2,3-dihydroxy ferruginol. Our study further suggests that the structure of the natural isolate by Chen and co-workers may differ from the originally proposed structure by Simoneit and co-workers. Based on these observations, we believe that the compound referred to as 2,3-dihydroxyferruginol isolated by Chen and co-workers may have a different structure, and we conclude that our synthesis corresponds to the 2,3-dihydroxyferruginol originally proposed by Simoneit and co-workers.

We further wanted to expand this strategy to the synthesis of ferruginol **3** by the diversification of the A- and C-rings of compound **8**. We began modifying intermediate **15**, which was first subjected to a Friedel–Crafts acylation reaction, followed by base-mediated methanolysis, to produce the acyl compound **27** in 90% yield over two steps. Subsequently, the secondary alcohol in **27** was mesylated and subjected to elimination using LiBr and Li$_2$CO$_3$. Under reflux conditions in DMF, both elimination and demethylation occurred simultaneously, resulting in the formation of compound **28** with a yield of 70%. Next, the ketone group was treated with methyl lithium to form the corresponding benzylic tertiary alcohol. The crude product obtained was further subjected to H$_2$ in the presence of Pd/C for benzylic deoxygenation and C–C double bond reduction to provide (+)-ferruginol **3** in 92% over two steps (Scheme 7). The spectral data of synthetic **3** was identical to the reported data, and the specific rotation $[\alpha]_D^{25}$ +41 (*c* 0.3, EtOH) is nicely aligned with the reported value {$[\alpha]_D^{16}$ +40.6 (*c* 0.14, EtOH)}.[13]

Scheme 5 Alternate route to the nagiol through α-oxygenation and diastereoselective reduction.

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Scheme 7 Synthesis of (+)-ferruginol (**3**).

Conclusion

In conclusion, we have accomplished the first enantioselective total synthesis of nagiol starting from 8,11,13-podocarpatriene-3-ol, along with a revision of its originally proposed structure. This synthetic strategy was further extended to the total synthesis of ferruginol and 2,3-dihydroxyferruginol. The enantiomerically enriched starting podocarpatriene-3-ol, consisting of the desired tricyclic framework, was efficiently synthesized and diversified to different diterpenes. The 2,3-dihydroxy functionality on the A-ring was introduced using two alternative methods: (i) an OsO$_4$-catalyzed stereoselective dihydroxylation of olefin, and (ii) α-oxygenation of a ketone using molecular oxygen and a base, followed by stereocontrolled reduction. Based on a detailed comparison of NMR data and supported X-ray analysis, the C-2β/C-3β syn-dihydroxy isomer was confirmed to be natural nagiol. The synthetic 2,3-dihydroxyferruginol was found to show a discrepancy in the spectral data with the reported data (by Chen and co-workers). However, we declare that we synthesized (+)-2,3-dihydroxyferruginol as per the Simoneit and Liang groups. Overall, the strategy features regioselective Friedel–Crafts acylations, a Baeyer–Villiger rearrangement, and regioselective elimination, stereoselective dihydroxylation, α-oxygenation of ketone, diastereoselective reduction of diketone, one-pot elimination and demethylation and hydrogenolysis reactions as key steps. In total, nagiol was synthesized in a short route in nine steps with seven step purifications in an overall yield of 35.5%.

Author contributions

GR and SS devised the idea, conducted experiments with help of AR. GR and SS prepared the manuscript and ESI.†

Conflicts of interest

There are no conflicts to declare.

Data availability

Experimental procedures and spectral data of all compounds are available as electronic ESI.†

X-Ray crystallographic data of compound **22** CCDC 2457373 is available in the ESI file.†

Acknowledgements

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