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Total Syntheses of the Tetracyclic Cyclopiane Diterpenes Conidiogenone, Conidiogenol, and Conidiogenone B

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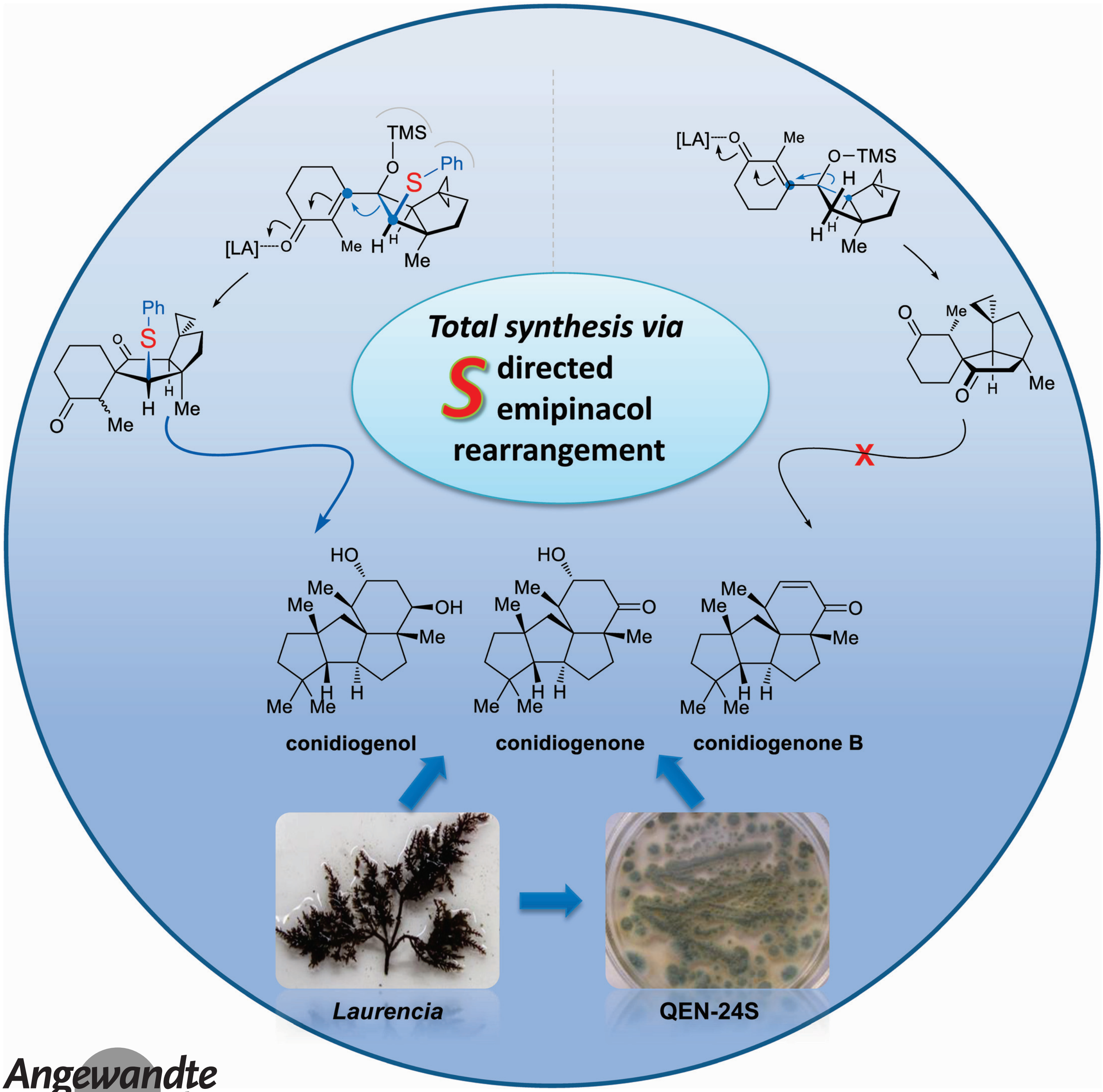
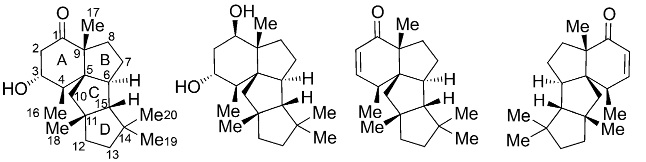


Abstract: *Total syntheses of the biologically important and structurally unique tetracyclic diterpenes conidiogenone, conidiogenol, and conidiogenone B of the cyclopiane class are reported. The absolute configuration of naturally occurring conidiogenone B was also corrected. The key step of our strategy involved the highly efficient construction of both ring C and the quaternary carbon center shared by rings A and C through a one-step regioselective and diastereoselective cycloenlargement in the form of a semipinacol-type rearrangement. In particular, the desired regioselectivity was made possible by properly adjusting the migratory aptitude of the migrating carbon atom through the introduction of an electron-donating phenylthio group at this position.*

Since 2002, a series of novel tetracyclic diterpenes of the cyclopiane class with some biologically important properties have been isolated and characterized, both from fermentation broths and marine-derived entophytic fungi of the *Penicillium* genus.[1] In particular, conidiogenone (**1**) and conidiogenol (**2**) (Scheme 1) exhibit potent conidiation-inducing activity (20 ng of **1** or **2** per milliliter of medium is enough for the total induction of conidiogenesis in the fermentation of *Penicillium cyclopium*).[1a] Conidiogenone B (**3**) also shows high antibacterial activity against methicillin-resistant *Staphylococcus aureus*, *Pseudomonas fluorescens*, *P. aeruginosa*, and *S. epidermidis*, in each case with a minimum inhibitory concentration of $8\,\mu g\,mL^{-1}$.[1c] However, only a trace amount of these natural compounds could be obtained by fermentation or from a marine source. For example, **1** (0.64 mg) was isolated from a 300 L fermentation broth of *Penicillium cyclopium*,[1a] and **3** (11.2 mg) was isolated from a 100 L fermentation broth of *Penicillium* sp.[1b] The absolute configuration of these compounds has not been determined, except that of **3**, which was deduced on the basis of circular dichroism (CD) spectroscopy (Scheme 1).[1b] To the best of our knowledge, there has not been any report so far about the total synthesis of this class of diterpenes.[2] The chemical synthesis of these molecules is highly desirable, not only to gain further insight into the conidiogenesis of related fermentation processes, but also to explore their potential use in pharmaceutical biotechnology, the food industry, and drug discovery.[3]



conidiogenone (-)-**1**

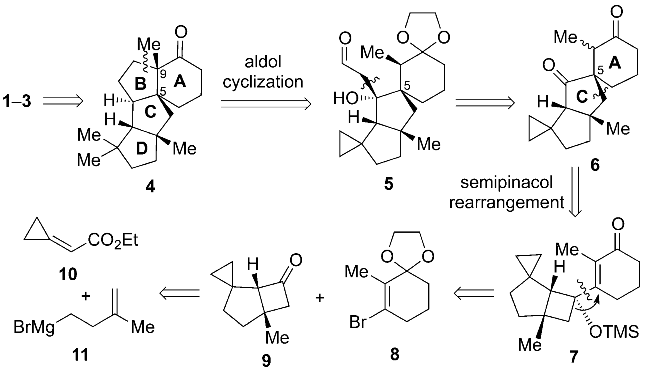
conidiogenol (-)-**2**

conidiogenone B (-)-**3**

proposed absolute configuration of conidiogenone B

Scheme 1. Representative bioactive tetracyclic diterpenes of the cyclopiane class.

Tetracyclic diterpenes of the cyclopiane class feature four highly fused and strained rings (A/B/C/D), 6–8 consecutive stereocenters, and four congested quaternary carbon centers.[4] Although a few strategies for constructing polycyclic systems with multiple stereocenters have been developed,[5] they are not applicable to the synthesis of an architecture as challenging as that of the cyclopiane diterpenes, which possess a particular pattern of rings and stereocenters. On the basis of our previously developed efficient methodologies for constructing all-carbon quaternary centers,[6] a vinyl cyclobutanol precursor was designed for the key cycloenlargement semipinacol-type rearrangement to construct the spirocyclic A/C ring system (Scheme 2). Herein, we report the rapid total syntheses of **1**–**3** as examples of this class of diterpenes and the confirmation of their absolute configuration as shown in Scheme 1.



Scheme 2. Retrosynthetic analysis of **1**–**3**. TMS = trimethylsilyl.

Our retrosynthesis (Scheme 2) showed that the target molecules **1**–**3** could be derived from a common tetracyclic core **4** through appropriate functionalization steps at a later stage. The strained B ring and quaternary C9 center of **4** could be constructed through intramolecular aldol cyclization of aldehyde **5**, which could be prepared from **6**. The C ring and spirocyclic quaternary center C5 of **6** would be constructed from the key vinyl cyclobutanol silyl ether precursor **7** through the crucial cycloenlargement semipinacol-type rearrangement.[6] Further disconnection of **7** gave the vinyl bromide **8**[7] and the key cyclopentane (ring D)-fused cyclobutanone intermediate **9**. Finally, **9** could be prepared from the known ester **10** and Grignard reagent **11** through 1,4-

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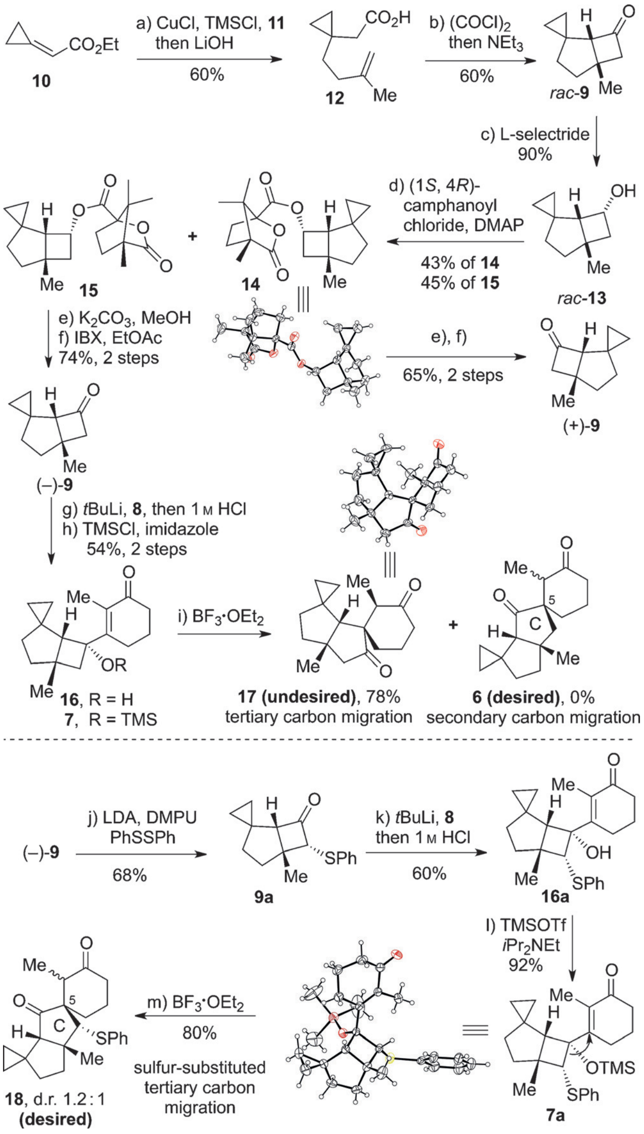
addition and intramolecular [2+2] cyclization. Because the steric hindrance of the *gem*-dimethyl group at ring D might influence subsequent transformations, the *gem*-dimethyl group was carried forward in the form of a spirocyclopropane and exposed at a later stage.

Our synthesis commenced with the preparation of the rearrangement precursor **7** from **10**[8] and **11**.[9] Treatment of the freshly prepared Grignard reagent **11** with ester **10** in the presence of CuCl and TMSCl, followed by the addition of LiOH, afforded acid **12** in 60% yield (Scheme 3). Intramolecular [2+2] cyclization of acid **12** under conditions reported by Ghosez and co-workers[10] then furnished the cyclobutanone *rac*-**9** in 60% yield. According to the reported absolute configuration of conidiogenone B (**3**),[1b] the chiral cyclobutanone derivative (−)-(*R*,*S*)-**9** was selected as the appropriate intermediate for our asymmetric synthesis. Unfortunately, attempts to synthesize (−)-**9** with high optical purity from **12** by the method described by Chen and Ghosez[10c] led to the product with only −60% *ee*. Therefore, we resorted to the chiral resolution of *rac*-**9**. For this purpose, the stereoselective reduction of *rac*-**9** with L-selectride afforded the alcohol *rac*-**13** as a single diastereoisomer, which was converted into a mixture of the diastereomeric esters **14** and **15** with (1*S*,4*R*)-camphanoyl chloride. The diastereoisomers **14** and **15** were separated chromatographically, hydrolyzed, and oxidized with IBX to give (+)- and (−)-**9** with an optical purity of 99% *ee*. The absolute configuration of **14** was confirmed by X-ray crystallographic analysis.[11] Subsequently, lithium–halogen exchange of **8** with *t*-BuLi gave the corresponding organolithium reagent, which was treated with ketone (−)-**9** to give the product **16** as a single diastereoisomer after quenching with aqueous HCl solution. Protection of the tertiary alcohol group afforded the rearrangement precursor **7** in 92% yield.

The cycloenlargement semipinacol-type rearrangement to construct ring C and the spirocyclic center (C5) gave rise to two possible challenges. First, two carbon atoms on the cyclobutanol moiety, the tertiary methine and the secondary methylene carbon atoms, can migrate, thus influencing the regioselectivity for the construction of ring C. Second, the diastereoselectivity for the generation of C5 depends on which C=C bond face is attacked by the migrating carbon atom. Unfortunately, initial tests of a semipinacol rearrangement of **7** with different Lewis acids ($BF_3{\cdot}OEt_2$, $TiCl_4$) always resulted in the undesired migration of the tertiary carbon atom to yield product **17**, and none of the desired product **6** was observed. The structure of **17** was confirmed by X-ray crystallographic analysis.[11]

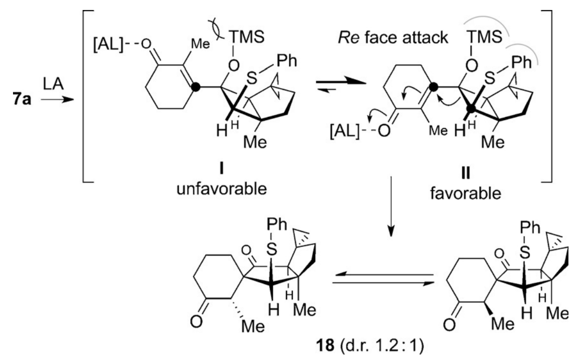


Scheme 3. Synthesis of the intermediate **18**. Reagents and conditions: a) CuCl, TMSCl, THF, −15 °C, then LiOH, THF/H_2O, 25 °C (60%); b) $(COCl)_2$, CH_2Cl_2, reflux, then NEt_3, toluene, reflux (60%); c) L-selectride, THF, −78 °C, then $NaBO_3{\cdot}4\,H_2O$, 0 °C (90%); d) (1*S*, 4*R*)-camphanoyl chloride, DMAP, CH_2Cl_2, 0 °C (**14**, 43%; **15**, 45%); e) K_2CO_3, MeOH, 25 °C; f) IBX, EtOAc, reflux ((+)-**9**, 65%, from **14** over 2 steps; (−)-**9**, 74%, from **15** over 2 steps); g) *t*BuLi, **8**, THF, −78 °C, then 1 M HCl/H_2O, 0 °C (63%); h) TMSCl, imidazole, CH_2Cl_2, 0→25 °C (85%); i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0→25 °C (78%); j) LDA, PhSSPh, DMPU, THF (68%); k) *t*BuLi, **8**, THF, −78 °C, then 1 M HCl/H_2O, 0 °C (60%); l) TMSOTf, *i*Pr_2NEt, CH_2Cl_2, 0 °C (92%); m) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0→25 °C (80%, d.r. 1.2:1). L-selectride = lithium tri-*sec*-butylborohydride, DMAP = 4-dimethylaminopyridine, IBX = 2-iodoxybenzoic acid, LDA = lithium diisopropylamide, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

To ensure that the migration of the secondary rather than the tertiary carbon atom in precursor **7** dominated, and hence the desired regioselectivity, we introduced a phenylthio group at the methylene carbon atom of **7** to enhance its electron density and increase its migratory aptitude.[12] Thus, (−)-**9** was treated with freshly prepared LDA and then PhSSPh to provide the thioether product **9a** in 68% yield (Scheme 3). The coupling of **8** with ketone **9a**, followed by deprotection of the ketal, gave the product **16a**. Protection of the tertiary alcohol with TMSOTf/*i*Pr_2NEt then afforded the designed precursor **7a** in 92% yield. The structure of **7a** was confirmed by X-ray crystallographic analysis.[11] By screening various reaction parameters of the semipinacol rearrangement of **7a**, including Lewis acids ($EtAlCl_2$, Et_2AlCl, $BF_3{\cdot}OEt_2$, $SnCl_4$, $TiCl_4$, $AlCl_3$), solvents (CH_2Cl_2, $ClCH_2CH_2Cl$, $CHCl_3$, THF, Et_2O, toluene), and temperatures (0 °C, 25 °C, −78 °C), we eventually found that the treatment of **7a** with $BF_3{\cdot}OEt_2$ in

CH_2Cl_2 afforded the desired product **18**,[13] which corresponds to **6**, in 80 % yield (d.r. 1.2 : 1).

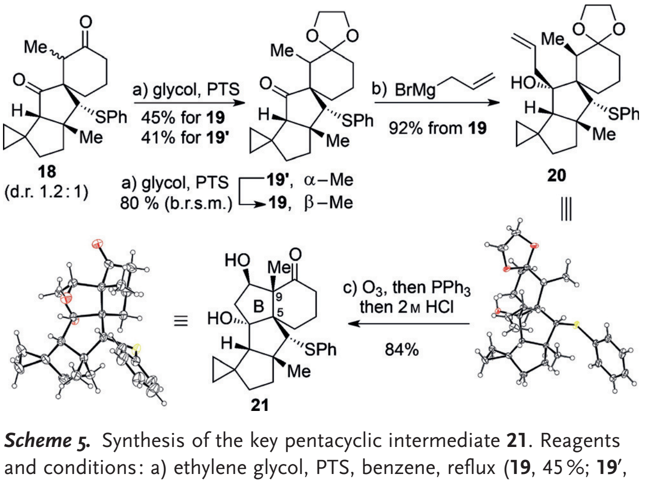
A mechanism for the stereospecific rearrangement to form the quaternary C5 center of **18** is proposed in Scheme 4. The migrating sulfur-substituted carbon atom can attack two possible faces of the C=C bond of **7a**. Steric hindrance between the methyl group on the cyclohexenone ring and the TMS group in conformer **I** prevents the rearrangement product forming. In conformer **II**, there is less steric hindrance limiting the desired rearrangement, which leads to the formation of the correct spirocyclic center (C5).



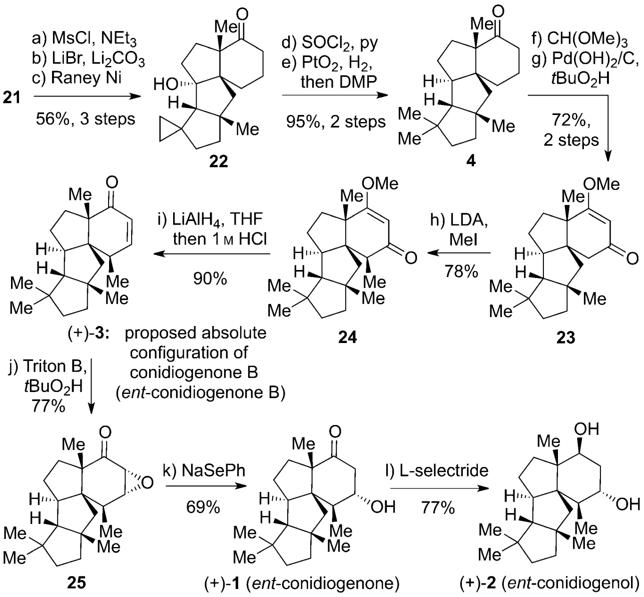
Scheme 4. Proposed mechanism for the formation of **18** from **7a**. LA = Lewis acid.

After successfully constructing the A/C/D rings and the quaternary carbon centers with the desired configuration, we focused our attention on building ring B and the quaternary C9 center through an aldol cyclization. Selective carbonyl protection of ketone **18** (d.r. 1.2 : 1) with glycol gave a separable mixture of ketal **19** and its isomer **19′** (1.1 : 1) (Scheme 5). Fortunately, isomer **19′** could be readily converted into **19** in 80 % yield based on recovered starting material (b.r.s.m.) through an in situ deprotection/protection procedure with glycol/PTS.[14] A subsequent reaction of **19** with allylmagnesium bromide afforded **20** in 92 % yield as a single diastereoisomer, whose structure was confirmed by X-ray crystallographic analysis.[11] Ozonization of the alkene **20** gave an aldehyde, which was directly subjected to an aldol cyclization in aqueous HCl to produce the desired intermediate **21** in 84 % yield; no other diastereoisomer was isolated. The structure of **21** was determined by X-ray crystallographic analysis.[11]

Subsequent functional-group transformations completed the total syntheses of the target diterpenes **1**–**3** (Scheme 6). Activation of the secondary OH group of **21** with methanesulfonyl chloride (MsCl) and elimination of MsOH with LiBr/Li_2CO_3, followed by reduction of the formed C=C bond and removal of the SPh group with Raney Ni, led to **22** in 56 % yield over three steps. Elimination of the tertiary OH group of **22**, exposure of the *gem*-dimethyl group with PtO_2/H_2, and oxidation with DMP then provided the ketone **4** in 95 % overall yield. The treatment of **4** with $CH(OMe)_3$/PTS in MeOH, followed by oxidation with $Pd(OH)_2/C$ and $tBuO_2H$ in the presence of Cs_2CO_3,[15] afforded the enone **23** in 72 % yield. The stereoselective methylation of enone **23** under LDA/MeI/HMPA conditions yielded **24**. Conidiogenone B (**3**) was produced from **24** in 90 % yield as a single diastereoisomer by reduction of the C=O bond with $LiAlH_4$ in THF. The NMR spectroscopic data of synthetic **3** agreed well with the data reported for the natural product, but its positive optical rotation and CD spectrum were opposite to those of the natural product.[16] On the basis of these observations and



Scheme 5. Synthesis of the key pentacyclic intermediate **21**. Reagents and conditions: a) ethylene glycol, PTS, benzene, reflux (**19**, 45 %; **19′**, 41 %; recovered material **18**, 11 %); b) allylmagnesium bromide, THF, 0 °C (92 %); c) O_3, CH_2Cl_2, −78 °C, then PPh_3, 0 °C, then 2 M HCl/H_2O, THF, 70 °C (84 %, one pot). PTS = *p*-toluenesulfonic acid.



Scheme 6. Completion of the synthesis of diterpenes **1**–**3**. Reagents and conditions: a) MsCl, NEt_3, CH_2Cl_2, 0 °C; b) LiBr, Li_2CO_3, DMF, 150 °C; c) Raney Ni, EtOH, 0 °C (56 %, 3 steps); d) py, $SOCl_2$, CH_2Cl_2, 0 °C; e) PtO_2, H_2 (1 atm), HOAc, EtOAc, 25 °C, then DMP, $NaHCO_3$, CH_2Cl_2, 0 °C (95 %, 2 steps); f) $CH(OMe)_3$, PTS, MeOH, reflux; g) $Pd(OH)_2/C$, $tBuO_2H$, Cs_2CO_3, CH_2Cl_2, 25 °C (72 %, 2 steps); h) LDA, MeI, HMPA, THF, −78 °C→25 °C (78 %); i) $LiAlH_4$, THF, 0 °C, then 1 M HCl/H_2O, 0 °C (90 %); j) Triton B, $tBuO_2H$, THF, 25 °C (77 %); k) PhSeSePh, $NaBH_4$, HOAc, EtOH, 0 °C (69 %); l) L-selectride, THF, −78 °C (77 %). DMF = *N*,*N*-dimethylformamide, py = pyridine, DMP = Dess–Martin periodinane, HMPA = hexamethylphosphoramide, Triton B = benzyltrimethylammonium hydroxide.

the absolute configuration of **14** as determined by X-ray diffraction,[11] the absolute configuration of naturally occurring conidiogenone B ((−)-**3**) should be modified to that shown in Scheme 1.

The epoxidation of enone (+)-**3** with Triton B and tBuO$_2$H gave the epoxide **25** in 77% yield (d.r. > 10:1). Reduction with with NaSePh[17] then afforded (+)-**1** as a single isomer. Further reduction of (+)-**1** with L-selectride furnished (+)-**2** in 77% yield (d.r. > 20:1). The respective NMR spectroscopic data of synthetically and naturally produced **1** and **2** agreed well. Conversely, the optical rotations of synthetic (+)-**1** and (+)-**2** were opposite to those of the natural products.[18] Therefore, the absolute configurations of naturally occurring conidiogenone ((−)-**1**) and conidiogenol ((−)-**2**) should be modified to those shown in Scheme 1.

In conclusion, we have completed the total synthesis of the cyclopiane class tetracyclic diterpene conidiogenone B (**3**) in 24 steps and transformed it into conidiogenone (**1**) and conidiogenol (**2**). The absolute configuration of naturally occurring **1**–**3** were also corrected through our syntheses. The significant feature of this strategy is that the key 6/5/5/5-fused tetracyclic framework and all quaternary centers of the diterpenes were rapidly constructed through intramolecular [2+2] cyclization, a regioselective and diastereoselective cycloenlargement semipinacol-type rearrangement, and subsequent aldol cyclization. These collective syntheses could provide a pathway for the construction of other cyclopiane class tetracyclic diterpene analogues. We are currently investigating the synthesis of analogues and the biological activity of these compounds.

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Keywords: cyclization · natural products · semipinacol rearrangement · tetracyclic diterpenes · total synthesis

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[13] Both the desired regioselectivity for the construction of ring C and the diastereoselectivity for the generation of the quaternary C5 center of compound **18** were confirmed by X-ray crystallographic analysis of its derivative **20** (Ref. [11]).

[14] For more details, see the Supporting Information.

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[16] Optical rotation of conidiogenone B (**3**): synthetic: $[\alpha]_D^{23.3} = +16.1$ ($c = 0.62$ in MeOH), $[\alpha]_D^{23.3} = +7.9$ ($c = 0.76$ in CHCl$_3$); natural: $[\alpha]_D^{20} = -6.0$ ($c = 0.55$ in MeOH). CD spectrum of conidiogenone B: synthetic (MeOH): λ_{max} ($\Delta\varepsilon$) = 230 (−16.9), 240 (−19.1), 308 (1.5), 348 nm (−5.1); natural (MeOH): λ_{max} ($\Delta\varepsilon$) = 194.2 (−8.0), 234.1 (2.0), 305.3 (−0.2), 347.0 nm (0.55).

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[18] Optical rotation of conidiogenone (**1**): synthetic: $[\alpha]_D^{23.3} = +35.9$ ($c = 0.39$ in CHCl$_3$); natural: $[\alpha]_D = -35.0$ ($c = 0.06$ in CHCl$_3$). Optical rotation of conidiogenol (**2**): synthetic: $[\alpha]_D^{23.3} = +14.0$ ($c = 0.57$ in CHCl$_3$); natural: $[\alpha]_D = -20.0$ ($c = 0.07$ in CHCl$_3$).

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