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Highly stereocontrolled total synthesis of secodolastane diterpenoid isolinearol†

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The first asymmetric total synthesis of isolinearol has been achieved with high stereoselectively. The synthetic method includes enatio- and diastereoselective reductive desymmetrization, stereocontrolled introduction of the methallyl group, regio- and stereocontrolled allylation and introduction of the side chain carbonyl group using olefin cross-metathesis with a pinacol vinyl boronic ester.

Marine brown algae of the genus *Dictyota*, belonging to the family Dictyotaceae, are a rich source of structurally diverse secondary metabolites possessing defensive properties that contribute to their successful survival in marine environments. Several diterpenes from the *Dictyota* species exhibit potent cytotoxic or antiviral activities which make them promising drug candidates due to their remarkable pharmacological activities.[1]

Isolinearol (**1**) was first isolated from the marine brown alga *Dictyota cervicornis* in 1986 by Teixeira *et al.* along with known related diterpenoids including linearol (**2**) and amijiol (**4**) (Fig. 1).[2] Compound **1** was subsequently isolated from *Dictyota indica* in 1990 by Ahmad *et al.* along with indicol (**3**) and indicarol acetate.[3] It was also isolated from the Brazilian brown alga *Canistrocarpus cervicornis*.[4] Isolinearol has a characteristic bicyclo[5.4.0]undecane carbon framework with a hemiacetal bridge and contains five stereocenters, including two all-carbon quaternary centers. The biological activity of isolinearol was not initially reported, however recently it was found that mixtures of linearol and isolinearol inhibited hemolysis and proteolysis caused by *B. jararaca* venom[5] and anti-herbivory activity.[6]

Some examples of the total synthesis of dolastane and secodolastane diterpenoids isoamijiol (**5**),[7,8] dolastatrienol (**6**),[8,9] 14-deoxyisoamijiol,[10] and indicol (**3**)[11] have been published its asymmetric total synthesis. To the best of our knowledge, and the absolute configuration of indicol (**3**) was determined by its asymmetric total synthesis. To the best of our knowledge, there have been no reports on the total synthesis of isolinearol (**1**), and its absolute configuration, although presumably the same as indicol, has not yet been determined.

The structural features and biological activities of **1** attracted our interest, and a synthetic study of isolinearol (**1**) was initiated. Our goal was to develop a stereocontrolled synthetic procedure to access isolinearol (**1**) and to extend the procedure to an asymmetric synthesis. Herein, we report the first total synthesis of isolinearol with high stereocontrol in both racemic and enantioenriched forms.

In this synthetic study, the key challenge is how to construct three continuous chiral centers on the cyclohexane ring and the all-carbon quaternary center on the cycloheptane ring with high stereoselectivity. Our retrosynthetic analysis of the total synthesis of **1** to address these issues is shown in Fig. 2. The final compound would be synthesized from diketone **7** by the removal of all protecting groups and the subsequent formation of a hemiacetal bridge. Diketone **7** would be obtained from ketone **8** by the regio- and stereocontrolled introduction of the side chain moiety to construct the all-carbon quaternary

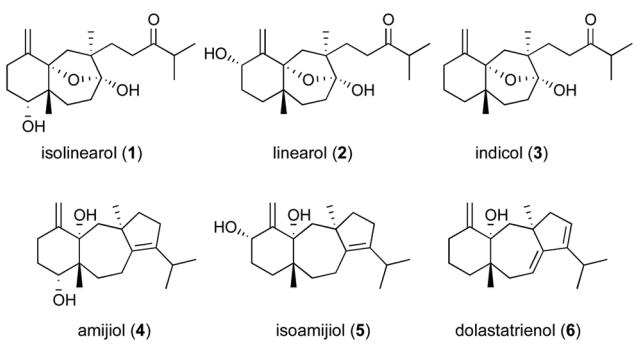

Fig. 1 Structures of isolinearol (**1**) and related diterpenoids **2**–**6**.

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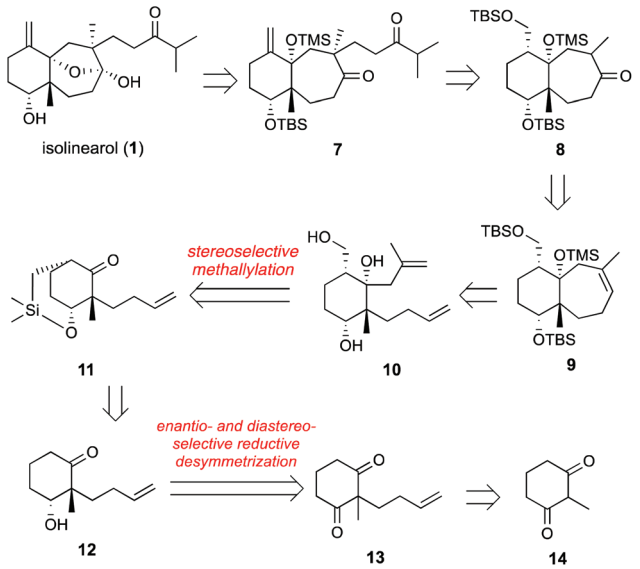
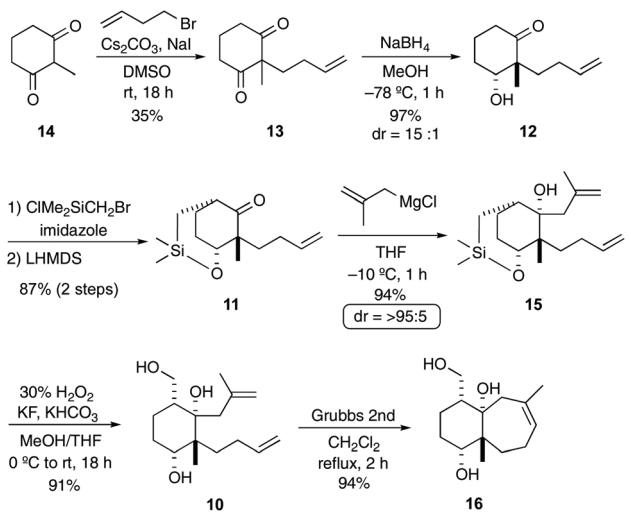


Fig. 2 Retrosynthetic analysis for the total synthesis of isolinearol (**1**).

center and form the *exo*-methylene. Ketone **8** would be derived from bicyclic compound **9**, which would be prepared from diene derivative **10** *via* ring-closing metathesis. Diene derivative **10** would be obtained by the stereocontrolled introduction of a methallyl group into the silicon-bridged compound **11**, which would be prepared from alcohol **12**. Alcohol **12** would be synthesized by a diastereoselective reductive desymmetrization of the symmetric diketone **13**. Symmetric diketone **13** could be derived from commercially available 2-methyl-1,3-cyclohexanedione (**14**).

Stereocontrolled construction of the contiguous chiral centers on the cyclohexane ring was the first aim of this synthetic project. The synthesis began with the commercially available 2-methyl-1,3-cyclohexanedione (**14**) as shown in Scheme 1.



Scheme 1 Stereocontrolled synthesis of bicyclic compound **16**.

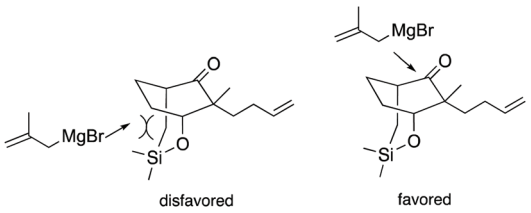
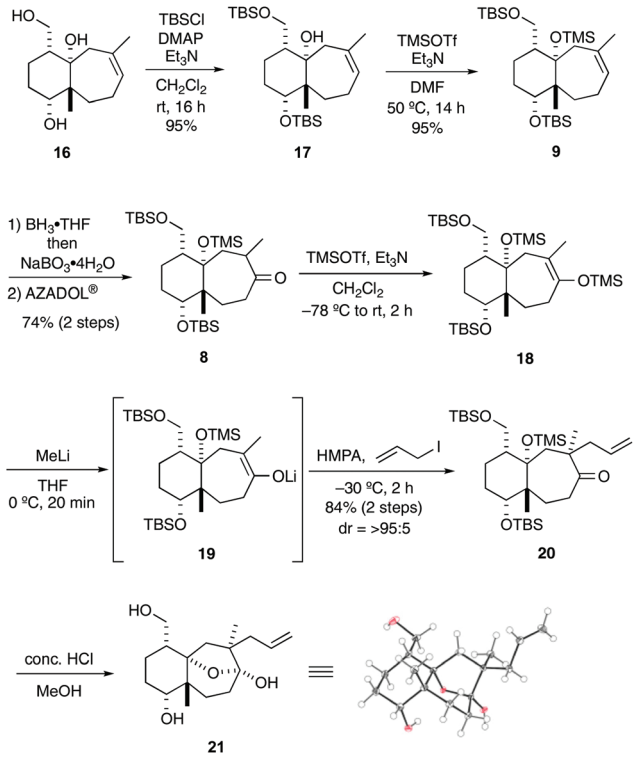


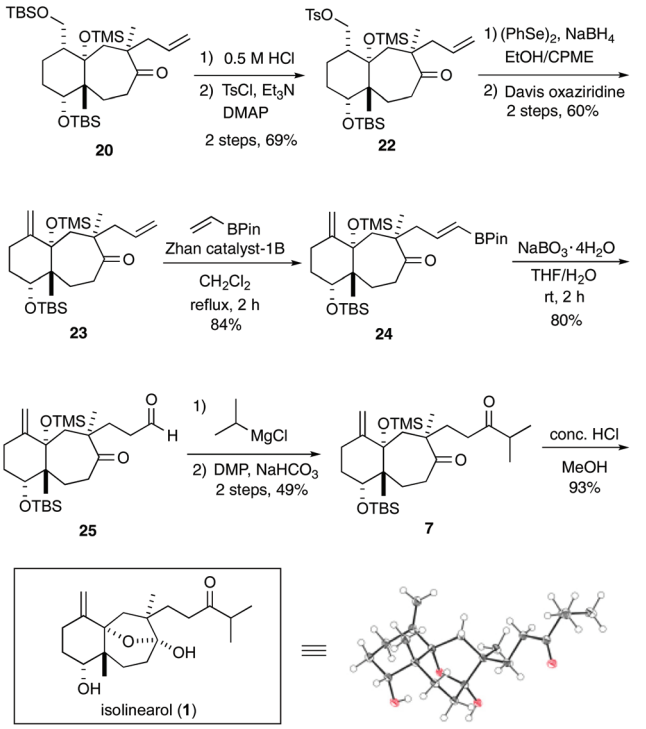
Fig. 3 Stereoselectivity of the methallylation of silicon-bridged compound **11**.

The introduction of the butenyl group into the activated methine of compound **14** gave the symmetric diketone **13** in 35% yield along with the *O*-butenyl compound in 30% yield. The diastereoselective reductive desymmetrization[12] of **13** was achieved using $NaBH_4$ in MeOH at −78 °C to provide the desired **12** in 97% yield with high diastereoselectivity. The silicon-bridged compound **11** was obtained according to Nakada's protocol.[13] Thus, treatment of **12** with $ClMe_2SiCH_2Br$ afforded the corresponding silyl ether in quantitative yield, then silicon bridge formation occurred by using LHMDS as a base to give compound **11** in 87% yield for the 2 steps. Methallyl group introduction into the silicon-bridged compound **11** using 2-methylallylmagnesium chloride provided the diene derivative **15** in 94% yield as a single diastereomer having the desired stereochemistry, as expected. We considered that the high stereoselectivity of the methallylation was due to the approach of the reagent from the opposite side of the silicon bridge (Fig. 3). Tamao oxidation of **15** provided the triol **10** in 91% yield and ring-closing metathesis of triol **10** using Grubbs second-generation catalyst provided the bicyclic compound **16** in 94% yield.

Having bicyclic compound **16** with the contiguous chiral centers in hand, we next focused on stereocontrolled construction of the all-carbon chiral center on the cycloheptane ring (Scheme 2). The primary and secondary alcohols of triol **16** were protected by TBS groups and the tertiary alcohol was protected by a TMS group to give compound **9** in 95% yield for 2 steps. The hydroboration–oxidation of **9** using BH_3·THF and $NaBO_3$·$4H_2O$ followed by oxidation of the resulting secondary alcohol using AZADOL®[14] afforded the ketone **8** in 74% yield for 2 steps. Then, in order to construct an all-carbon chiral center on the cycloheptane ring, we attempted several reaction conditions. As the results, we found out the allylation *via* silyl enol ether **18** was the suitable condition for this object. Thus, treatment of the ketone **8** with TMSOTf and Et_3N in CH_2Cl_2 provided more highly substituted trimethylsilyl enol ether **19**, which was converted to the lithium enolate by adding MeLi at 0 °C in THF, and then the addition of allyl iodide and HMPA at −30 °C afforded the desired compound **20** as the sole product. The stereochemistry of compound **20** was determined by X-ray crystallographic analysis of compound **21**,[15] which was derived from **20** by deprotection of the silyl groups followed by hemiacetal formation. The high stereoselectivity of the allylation was assumed to be due to the approach of the reagent to avoid the trimethylsilyl group present on the α-face.



Scheme 2 Stereocontrolled construction of the all-carbon quaternary chiral center on the cycloheptane ring.

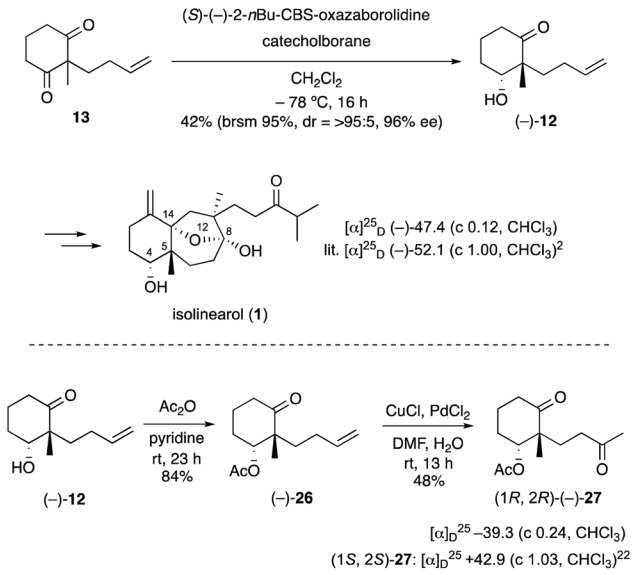


Scheme 3 Total synthesis of isolinearol (**1**).

After the successful construction of the all-carbon chiral center on the cycloheptane ring, our interest turned to the completion of the total synthesis of target molecule **1** (Scheme 3). First, after several attempts, the construction of the *exo*-methylene group was achieved by *syn*-elimination of a selenoxide using a four-step conversion as follows. Thus, the selective deprotection of the TBS ether using 0.5 M HCl followed by tosylation of the resulting primary alcohol provided compound **22** in 69% yield for 2 steps. The transformation of tosylate **22** to corresponding selenide was carried out under heating conditions (100 °C) in a mixed solvent of EtOH and cyclopentyl methyl ether using NaSePh generated *in situ* by the reaction of $(PhSe)_2$ with $NaBH_4$.[16] Oxidation of the obtained selenide using the Davis oxaziridine followed by *syn*-elimination of the resulting selenoxide provided the desired *exo*-methylene compound **23** in 60% yield for 2 steps. Next, the conversion of the terminal olefin to an aldehyde for construction of the side chain was investigated. As a result, the synthesis of aldehyde **25** was achieved by the olefin cross-metathesis of **23** with pinacol vinyl boronic ester[17] in the presence of Zhan catalyst-1B,[18] followed by oxidation of the resulting vinyl boronic ester **24** using $NaBO_3{\cdot}4H_2O$. Compound **7** possessing the side chain moiety was successfully obtained from **25** *via* the aldehyde–selective introduction of an isopropyl group and oxidation of the resulting secondary alcohol with DMP in 85% yield. Finally, upon treatment of **7** with conc. HCl in MeOH for 10 h at room temperature, deprotection of the TBS and TMS groups and formation of the hemiacetal bridge proceeded simultaneously, and the target molecule **1** was obtained in 93% yield as the sole product. Both ^1H and ^{13}C NMR spectra of the synthetic compound **1** were identical to those of the reported natural isolinearol.[2] Additionally, the structure of compound **1** was unambiguously confirmed by X-ray crystallographic analysis.[19]

Thus, we achieved the total synthesis of isolinearol (**1**) in racemic form. The remaining challenges were the asymmetric synthesis and verification of the absolute configuration of isolinearol (**1**). According to our synthetic route, in order to synthesize optically active isolinearol (**1**), compound **12** must be obtained in optically active form. After several attempts at the asymmetric reductive desymmetrization of **13**, we found that the Corey–Bakshi–Shibata (CBS) reduction[20] was suitable to obtain the optically active **12** with high enantiomeric excess (Scheme 4). Thus, the CBS reduction of **13** using (*S*)-2-*n*-Bu-CBS-oxazoborolidine and catecholborane afforded **12** in satisfactory yield (42%, brsm 95%) in 91% ee[21] as a single diastereomer. In order to determine the absolute configuration, compound **12** was transformed to known compound **27**[22] *via* acetylation of the secondary alcohol and Wacker oxidation of the terminal olefin. The optical rotation of synthetic **27** had the opposite rotation to that reported in the literature [synthetic **27**: $[\alpha]_D^{25}$ −39.3 (*c* 0.24, $CHCl_3$); reported (1*S*,2*S*)-**27**: $[\alpha]_D^{25}$ +42.9 (*c* 1.03, $CHCl_3$)[22]]. Therefore, the absolute configuration of (−)-**12** was assigned as 1*R*,2*R*.

With the optically active **12** in hand, the asymmetric synthesis of isolinearol (**1**) through the established procedure was attempted. Both ^1H and ^{13}C NMR spectra of synthetic **1** were identical with those of natural isolinearol (**1**) and the optical



Scheme 4 Asymmetric total synthesis of (–)-isolinearol (**1**).

rotation of synthetic **1** had the same rotation as that reported for the natural product [synthetic **1**: $[\alpha]_D^{25}$ −47.4 (*c* 0.12, $CHCl_3$); natural product **1**: $[\alpha]_D^{25}$ −52.1 (*c* 1.00, $CHCl_3$) [2]. Therefore, we have determined the absolute configuration of natural isolinearol as expected [4*R*,5*R*,8*R*,12*R*,14*S*].

Conclusions

In conclusion, the first total synthesis of racemic isolinearol (**1**) was accomplished from the commercially available 2-methyl-1,3-cyclohexanedione in a total of 22 steps. The overall yield was 1.7% from 2-methyl-1,3-cyclohexanedione (**14**). This synthesis included the following features: (i) construction of three contiguous chiral centers on the cyclohexane ring utilizing diastereoselective reductive desymmetrization of 2-butenyl-2-methyl-1,3-cyclohexanedione and stereocontrolled introduction of a methallyl group into the silicon-bridged compound; (ii) construction of the quaternary carbon chiral center using regio- and stereocontrolled allylation *via* a silyl enol ether derivative; and (iii) introduction of the side chain carbonyl group using olefin cross-metathesis with pinacol vinyl boronic ester followed by oxidation. In addition, we achieved the asymmetric total synthesis of **1** using CBS reduction in the asymmetric reductive desymmetrization of the 1,3-cyclohexanedione derivative and determined its absolute configuration. Our methodology can be extended to the synthesis of dolastane and secodolastane diterpenoids. Further investigations are now in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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