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Enantiocontrolled synthesis of C-19 tetrahydrofurans isolated from the marine alga *Notheia anomala*

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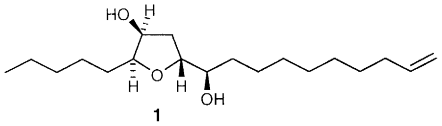
Abstract

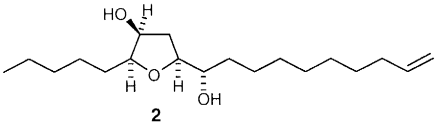
The stereocontrolled synthesis of (2*S*,3*S*,5*R*)-5-[(1*R*)-1-hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol and (2*S*,3*S*,5*S*)-5-[(1*S*)-1-hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol, both isolated from the brown alga *Notheia anomala* has been achieved. The requisite configurations of the stereogenic centres were established by Sharpless asymmetric dihydroxylation and Katsuki–Sharpless asymmetric epoxidation.

Keywords: marine metabolites; asymmetric synthesis; enantiopure functionalized tetrahydrofurans.

(2*S*,3*S*,5*R*)-5-[(1*R*)-1-Hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol (**1**)[1] and (2*S*,3*S*,5*S*)-5-[(1*S*)-1-hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol (**2**),[2] which have a characteristic substitution pattern in their tetrahydrofuran ring system, are C_{19} diols isolated from *Notheia anomala*, a member of the Notheiaceae family, a taxonomically unique brown alga found along the southern Australian coasts. These tetrahydrofurans have been considered to be biosynthesized via a cyclization of a natural methylene-interrupted bisepoxide and, within this context, a biomimetic synthesis of the racemic compounds has been reported.[3] On the other hand, both **1** and **2** are potent and selective inhibitors of the larval development of parasitic nematodes.



1



2

Considerable efforts have been directed to the synthesis of **1**[4] but, to the best of our knowledge, no enantiomeric synthesis of **2** has hitherto been reported. Within our general program directed at the enantiomeric synthesis of bioactive substances of marine origin,[5] we focused our attention on the above-mentioned compounds as examples of metabolites containing a highly functionalized tetrahydrofuran

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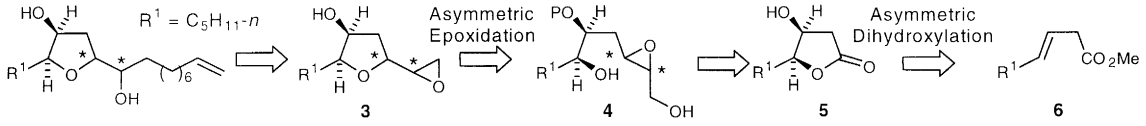
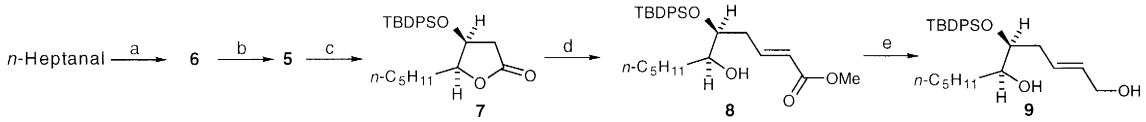
ring. In this communication, we describe our approach to the enantiomeric synthesis of these compounds, based on the retrosynthetic analysis outlined in Scheme 1. We considered a general methodology that would permit the selection of the stereochemistry in the ring formation in a simple manner. Thus, we first disconnected the unsaturated chain to the terminal epoxide **3**, bearing in mind the possibility of introducing such a chain by a nucleophilic opening of the terminal ring. This epoxide with the correct stereochemistry would be built from suitable 2,3-epoxy alcohol **4**, available by a Katsuki–Sharpless asymmetric epoxidation (AE)[6] of the corresponding allylic alcohol obtained by homologation from a γ-lactone such as **5**, which should be easily synthesized by Sharpless asymmetric dihydroxylation (AD)[7] of the corresponding β,γ-unsaturated ester **6**.[8]



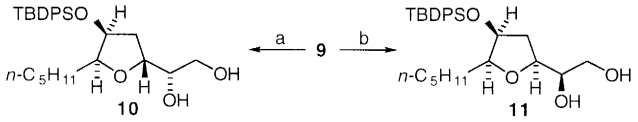
Scheme 1.

Our synthesis of **1** and **2** started with the unsaturated ester **6**, available by a modified Knoevenagel condensation of malonic acid and *n*-heptanal (Scheme 2).[9] The application to **6** of the AD reaction using AD-mix-α provided the γ-lactone **5** in 96% ee, in accordance with the NMR analysis of the corresponding Mosher's esters.[10] With these steps we simultaneously achieved two important goals: firstly, we introduced the correct stereochemistry in two stereocentres of the final molecules, and secondly, by the lactonization we performed the chemical differentiation between the two hydroxy groups. The protection of the free secondary hydroxy group led to the silyl ether **7** that was converted to the *E*-unsaturated ester **8** by selective reduction to the corresponding lactol followed by a Horner–Wadsworth–Emmons reaction. The reduction of **8** provided the allylic alcohol **9**, useful to introduce the remaining stereocentres.



Scheme 2. Reagents and conditions: (a) (i) malonic acid, piperidine (cat.), xylene, reflux, 3 h; (ii) TMSCl, MeOH, rt, 2 h, 80% overall; (b) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH:H_2O (1:1), 0°C, 20 h, 82%; (c) TBDPSCl, imidazole, CH_2Cl_2, rt, overnight, 96%; (d) (i) DIBAL-H (1 equiv.), ether, −78 °C, 5 min; (ii) $Ph_3P{=}CHCO_2Et$, benzene, 50°C, 2 h, 89% overall; (e) DIBAL-H, ether, 0°C, 5 min, 77%

At this step of the synthesis we pondered a divergent strategy to access either **1** or **2**, simply choosing the suitable reagent in the next stereoselective reaction. Thus, the asymmetric epoxidation of **9** using (*R*,*R*)-(+)-DET provided by concomitant epoxide opening[11] the *anti*-tetrahydrofuran **10** as the sole detected stereoisomer, while the use of the enantiomeric chiral auxiliary provided the corresponding *syn*-diastereoisomer **11**.[12] In both cases, we constructed the desired tetrahydrofurans having controlled three of the required stereocentres (Scheme 3).

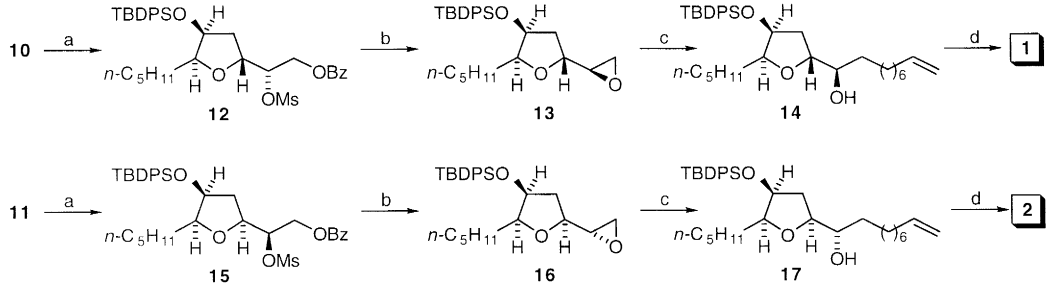


Scheme 3. Reagents and conditions: (a) Ti(OPr-*i*)$_4$, (*R*,*R*)-(+)-DET, TBHP, CH_2Cl_2, −20°C, 2 h, 82%; (b) Ti(OPr-*i*)$_4$, (*S*,*S*)-(−)-DET, TBHP, CH_2Cl_2, −20°C, 2 h, 82%

In order to fulfil the synthesis of natural compounds, first we addressed our efforts to the synthesis of **1**. Thus, the diol **10** was monoprotected as the benzoyl ester and the secondary free alcohol was transformed

into the corresponding mesylate **12**. Basic hydrolysis of the ester then provided the terminal epoxide **13** by intramolecular displacement of the secondary mesylate group with the primary alkoxide. Opening of the terminal epoxide with the Grignard reagent derived from commercially available 8-bromo-1-octene, in the presence of CuI, furnished compound **14** that after cleavage of the silyl protecting group provided (2*S*,3*S*,5*R*)-5-[(1*R*)-1-hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol (**1**), mp 50–52°C, $[\alpha]_D^{25}$=+15.2 (*c* 0.8, $CHCl_3$).[13]

With these satisfactory results in our hands, the synthesis of the diastereoisomer **2**, mp 35–37°C, $[\alpha]_D^{25}$=+20.5 (*c* 0.4, $CHCl_3$),[14] was performed in a straightforward and similar manner from **11** (Scheme 4).



Scheme 4. Reagents and conditions: (a) (i) BzCl (1.2 equiv.), TEA, CH_2Cl_2, 0°C, 2 h, (ii) MsCl, TEA, 0°C, 15 min, 75%; (b) NaH, MeOH, CH_2Cl_2, 0°C, 30 min, 80%; (c) H_2C=CH–$(CH_2)_7$MgBr, CuI, THF, –30°C; (d) TBAF, THF, rt, 1 h, 78%

In summary, we have developed a divergent route to *anti*- or *syn*-2-hydroxy-2,5-dialkyltetrahydrofurans from a common precursor. The application of two consecutive enantioselective reactions ensures very high enantiomeric purity in the final products. Moreover, the described methodology can be applied to other natural products with a similar structure.

Acknowledgements

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12. Although the enantiomeric excess of **5** was 96% ee, we did not observe any other diastereoisomer. We also checked the Mosher's diesters of **10** and found no traces of the enantiomer. We concluded that at this stage of the synthesis our product could be considered as a pure enantiomer, at least within of the limits of accuracy of NMR analysis.
13. The reported data for natural **1** (Ref. 1) are mp 54.5–55.0°C, $[\alpha]_D$=+15 (*c* 1, $CHCl_3$).
14. (2*S*,3*S*,5*S*)-5-[(1*S*)-1-Hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol (**2**) was reported (Ref. 2) upon isolation as a colorless oil $[\alpha]_D$=+75.5 (*c* 0.4, $CHCl_3$). Although the spectroscopic data coincide with those reported, the discrepancy with our specific rotation value suggests the necessity to reisolate the natural compound in order to perform a comparative study.