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Enantioselective total synthesis of idesolide via $NaHCO_3$-promoted dimerization

Tomohiro Nagasawa, Naoyuki Shimada, Munefumi Torihata, Shigefumi Kuwahara *

Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan

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ABSTRACT

The enantioselective total synthesis of idesolide has been accomplished in 20% overall yield from a known allylic alcohol by a nine-step sequence involving the Sharpless asymmetric epoxidation as the source of chirality and an efficient $NaHCO_3$-promoted dimerization of the monomeric form of idesolide as the key transformation.

1. Introduction

In their search for antiinflammatory substances from natural sources, Kim and co-workers isolated an inhibitor of lipopolysaccharide-induced nitric oxide (NO) production in BV2 microglial cells from the fresh fruits of *Idesia polycarpa*, a deciduous tree native to East Asian countries.[1] Based on extensive spectroscopic analyses coupled with X-ray crystallography, they determined the structure of the NO production inhibitor as **1**, albeit without assignment of its absolute configuration, and named it idesolide (Fig. 1). Recently, idesolide (**1**) was also shown to improve hippocampus-dependent recognition memory in rodents, indicating its potential as a therapeutic drug for memory-related brain anomalies such as mild cognitive impairment (MIC) and Alzheimer's disease.[2] From a structural viewpoint, idesolide (**1**) characterized by a unique spirocyclic architecture embedded with a tetrahydrobenzodioxole ring is an unsymmetrical dimer of its monomeric form **2**,[3] which has also been isolated as a natural product or found as a component of more complex natural products produced by willows and poplars.[4] Recently, Snider and co-workers achieved the first synthesis of the monomer **2** in both racemic and optically enriched forms and attempted its dimerization to idesolide (**1**).[5] All of their efforts to dimerize **2** into **1** were, however, unsuccessful, suggesting the presence of a significant kinetic barrier to the formation/decomposition of idesolide (**1**). This difficulty was overcome by Iwabuchi and co-workers' serendipitous discovery that the dimerization of **2** was significantly promoted by AZADO[6] and some tertiary amines, which enabled them to complete the first total synthesis of **1** and determine its absolute configuration.[7] Prompted by the unique structure and the interesting biological activity of **1**, we also embarked on its total synthesis. The present article describe a new enantioselective total synthesis of **1** using the Sharpless asymmetric epoxidation as the source of chirality and an efficient $NaHCO_3$-promoted dimerization of **2** into **1** as the key transformation.

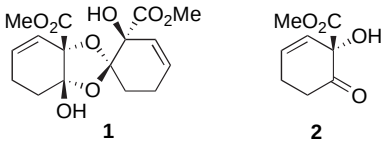

Figure 1. Idesolide (**1**) and its monomeric form (**2**).

2. Results and discussion

Our retrosynthetic analysis of **1** is shown in Scheme 1. Assuming that idesolide (**1**) should be formed from two molecules of its monomeric form **2** via unsymmetrical acetal/hemiacetal formation,[8] we set the preparation of the monomer **2** as our first task. Compound **2** would be obtainable by β-eliminative epoxide ring opening of **3**, which in turn could be derived from epoxy alcohol **4** via oxidation and subsequent methyl esterification. To obtain **4**, we planned to use the Sharpless asymmetric epoxidation of known allylic alcohol **5**.

According to our synthetic plan, the starting material **5**, obtained by the Morita/Baylis/Hillman reaction of 2-cyclohexenone

* Corresponding author. Tel./fax: +81 22 717 8783; e-mail address: skuwahar@biochem.tohoku.ac.jp (S. Kuwahara).

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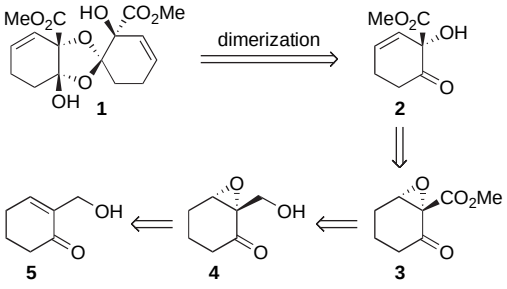
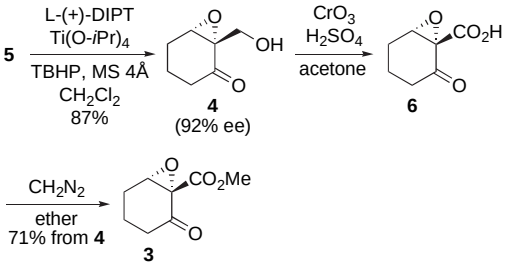


Scheme 1. Retrosynthetic analysis of **1**.

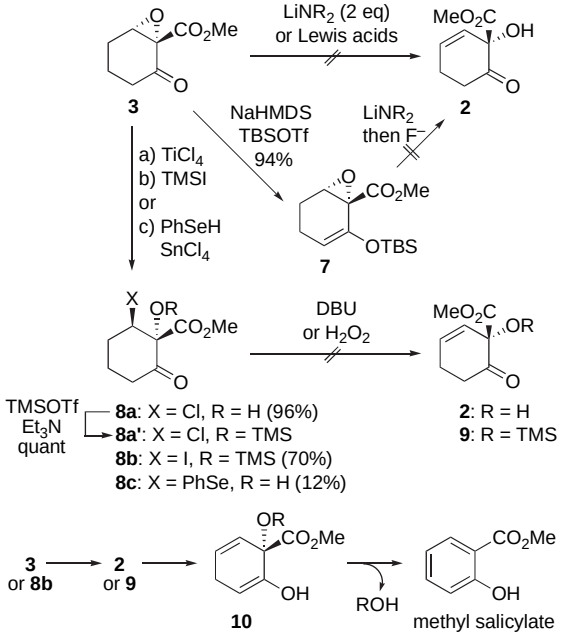
with formaldehyde,[9] was subjected to the Sharpless asymmetric epoxidation to give **4** in 87% yield and 92% enantiomeric excess (Scheme 2). The epoxy alcohol **4** was then oxidized with Jones reagent, and the resulting carboxylic acid **6** was esterified with diazomethane to afford the epoxy keto ester **3**.



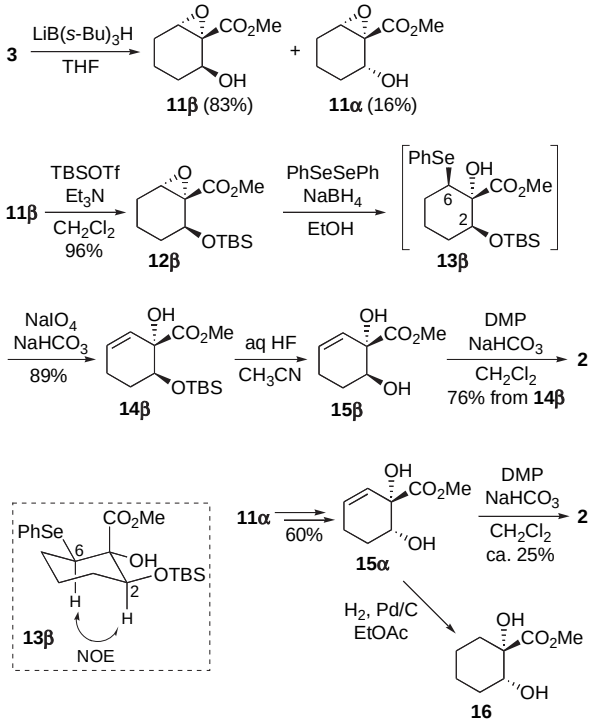
Scheme 2. Preparation of intermediate **3**.

To obtain the idesolide monomer **2** from **3** in a single step, we first attempt the β-eliminative ring opening of the epoxide **3** using LDA, LHMDS, or LTMP as the base (2 equiv) in the presence or absence of HMPA at a wide range of temperatures (−78 to 0 °C) in THF (Scheme 3). All of the attempts were, however, unsuccessful, resulting in the formation of complex mixtures. Lewis acid-promoted direct isomerization of **3** into **2** (or its TMS ether) using such reaction conditions as $LiClO_4$/toluene,[10] Bu_2BOTf/DBU/CH_2Cl_2,[11] TMSOTf/2,6-lutidine/CH_2Cl_2,[12] and $Mg(ClO_4)_2$/toluene[13] also brought no fruitful outcome, affording the aromatization product, methyl salicylate, in most cases. Exposure of TBS enol ether **7**, prepared by treating **3** with NaHMDS/TBSOTf in THF, to basic conditions (LHMDS/THF, LTMP/THF, or LDA/*t*-BuOK/THF[14]) followed by desilylation was also unsuccessful. Faced with the difficulty in the β-eliminative epoxide ring opening, we next attempted two-step procedures consisting of epoxide ring opening of **3** with a nucleophilic species (X^-) and subsequent base-induced β-elimination of HX. The ring opening of the epoxide **3** proceeded smoothly by its treatment with $TiCl_4$ in CH_2Cl_2[15] and TMSI in CH_2Cl_2,[16] giving **8a** and **8b**, respectively, the former of which was then further transformed quantitatively into the corresponding TMS ether **8a′**. Treatment of **8a**, **8a′**, and **8b** with DBU in CH_3CN, CH_2Cl_2, or toluene in the presence or absence of $AgClO_4$, however, yielded neither the desired product **2** nor its TMS ether derivative **9**; substrates **8a** and **8a′** merely afforded **3**, and a mixture of **3** and **8a**, respectively, as identifiable products, while **8b** gave methyl salicylate when treated with DBU in CH_3CN at 70 °C. Oxidative elimination (aq H_2O_2/$NaHCO_3$ in THF) of β-hydroxy selenide **8c** obtained in low yield by treating **3** with PhSeH and $SnCl_4$ in CH_2Cl_2[17,18] also resulted in the formation of a complex mixture containing only a trace amount of **2**. Although the transformation of **3** into **2** was found to be troublesome, the isolation of methyl salicylate in the Lewis acid-promoted isomerization of **3** as well as in the β-elimination of **8b** led us to suspect that the generation of methyl salicylate might have proceeded via initial formation of **2** or **9** by β-elimination of **3** or **8b**, followed by undesired enolization of the ketone function and subsequent 1,4-elimination of H_2O or TMSOH from the resulting skipped diene **10**.[19] These considerations made us take an alternative approach to **2** using an alcohol intermediate instead of the ketone intermediates **3** and **8**.

In line with the discussion described above, the ketone **3** was reduced with LiB(*s*-Bu)$_3$H to give epoxy alcohols **11β** and **11α** in yields of 83% and 16%, respectively (Scheme 4).[20] The major epimer **11β** was then protected as its TBS ether and the product **12β** was treated with PhSeSePh and $NaBH_4$ in EtOH to give β-hydroxy selenide **13β**.[18a] The selenide was subjected, in one pot, to oxidative elimination conditions to afford allylic alcohol **14β** in 89% yield from **12β**. The intermediate **13β** was stable enough to be isolated



Scheme 3. Attempts for the conversion of **3** into **2**.

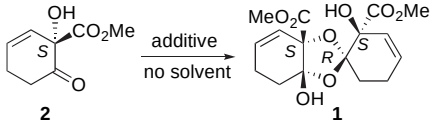


Scheme 4. Successful transformation of **3** into **2**.

and analyzed by ^{1}H NMR, enabling us to determine the 2,6-*cis* stereochemistry by observing a NOE correlation between the hydrogens at the C2 and C6 positions (see the conformational diagram in Scheme 4). Finally, removal of the TBS protecting group and subsequent oxidation of the resulting *trans* diol **15β** with the Dess/Martin periodinane furnished the idesolide monomer **2**. The minor epimer **11α** formed in the reduction of **3** could also be transformed into **2** via **15α** by following the same reaction sequence as used for the conversion of **11β** into **2**, although the final oxidation step for the conversion of the *cis* diol **15α** into **2** resulted in a low yield of 25%, presumably due to the C–C bond cleavage of the vicinal diol moiety.[21] The absolute configuration of **15α** was confirmed by reducing it into known dihydroxy ester **16** and comparing its specific rotation with a reported value.[22,23]

With the idesolide monomer **2** in hand, we proceeded to its dimerization to complete the total synthesis of **1**. Unlike previous investigations by Iwabuchi and co-workers, which focused mainly on the use of amines as the dimerization promoter,[7] we examined the effect of inorganic salts on the dimerization reaction. As shown in Table 1, no product was produced without additives (entry 1). The use of finely-powdered NH_4Cl as an acid catalyst also did not induce the dimerization, which is comprised of two consecutive hemiacetalizations (entry 2). Gratifyingly, however, when **2** was mixed with $NaHCO_3$ powder as a base catalyst and stirred (or left to stand)

Table 1
Dimerization of **2** into idesolide (**1**)

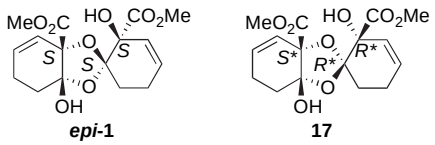


2 **1**

Entry	Additive	Temp	Time	Calcd yield[a] (%)		
				1	*epi*-**1**	**17**
1	None	5 °C	2 d	0	0	0
2	NH_4Cl (1 equiv)	5 °C	20 h	0	0	0
3	$NaHCO_3$ (1 equiv)	5 °C	20 h	39	3	7
4	$NaHCO_3$ (1 equiv)	rt	20 h	51	5	8
5	$NaHCO_3$ (2 equiv)	rt	20 h	65	4	7

[a] Determined by ^{1}H NMR.

at 5 °C for 20 h,[24] the formation of a substantial amount of **1** (39%, calculated from the ^{1}H NMR spectrum of the crude reaction mixture) as well as small amounts of *epi*-**1**, and heterodimer **17** [originating from the incomplete enantiomeric excess (92% ee) of the substrate **2**] was observed (entry 3, Fig. 2).[25] Raising the reaction temperature from 5 °C to room temperature (ca. 15–20 °C) was found to be effective to promote the dimerization, furnishing **1** in 51% yield, (entry 4). Furthermore, addition of an increased amount of $NaHCO_3$ (2 equiv) gave a better yield of 65% (entry 5), which enabled us to isolate **1** in 60% yield by flash column chromatography.[26] The improvement in the yield may be ascribable to the increase in the interfacial area between the liquid substrate and solid $NaHCO_3$, which is considered to be the site for the reaction to occur. The ^{1}H and ^{13}C NMR spectra of **1** were identical with those previously reported, and the specific rotation and melting point of **1** also showed good agreement with reported data.[1,7]



***epi*-1** **17**

Figure 2. Minor products in the dimerization of **2**.

3. Conclusion

The enantioselective total synthesis of (−)-idesolide (**1**), featuring the Sharpless asymmetric epoxidation as the chirality-inducing step and the use of $NaHCO_3$ as an efficient dimerization promoter of the idesolide monomer **2**, has been accomplished from the known allylic alcohol **5** in 20% overall yield through a nine-step sequence.

4. Experimental

4.1. General

IR spectra were recorded by a Jasco FT/IR-4100 spectrometer using an ATR (ZnSe) attachment. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian MR-400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Optical rotation values were measured with a Jasco DIP-371 polarimeter, and the mass spectra were obtained with Jeol JMS-700 spectrometer operated in the EI or FAB mode. Melting points were determined with a Yanaco MP-J3 apparatus and are uncorrected. Merck silica gel 60 (7–230 mesh) was used for column chromatography unless otherwise stated. Solvents for reactions were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 and CH_3CN from CaH_2; EtOH from Na and diethyl phthalate. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere.

*4.1.1. (1S,6S)-1-(Hydroxymethyl)-7-oxabicyclo[4.1.0]heptan-2-one (**4**).* To a stirred suspension of pulverized 4 Å molecular sieves (12.0 g), L-(+)-diisopropyl tartrate (9.00 mL, 42.8 mmol) and Ti(O*i*-Pr)$_4$ (13.0 mL, 41.7 mmol) in CH_2Cl_2 (100 mL) was added a solution of **5** (3.59 g, 28.5 mmol) in CH_2Cl_2 (35 mL) at −20 °C. After 30 min, the mixture was cooled to −30 °C and a solution of TBHP (5.60 M in toluene, 15.5 mL, 86.8 mmol) was added dropwise. The mixture was gradually warmed to −17 °C and stirred for 20 h before being quenched with $FeSO_4\cdot 7H_2O$ (24.0 g) and 10% aq tartaric acid (150 mL). The resulting mixture was filtered and the filtrate was extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=2:1–1:1) to give 3.52 g (87%) of **4** as a colorless oil. $[\alpha]_D^{21}$ −87.4 (*c* 1.23, $CHCl_3$); IR: ν_{max} 3418 (br s), 2881 (m), 1699 (vs), 1045 (s), 878 (w); ^{1}H NMR: δ 1.65–1.76 (1H, m), 1.89–2.03 (2H, m), 2.07–2.17 (1H, m), 2.22–2.33 (1H, m), 2.58 (1H, dm, *J*=17.6 Hz), 2.63–2.68 (br m, OH), 3.66 (1H, br s), 3.86 (1H, dd, *J*=12.9, 5.2 Hz), 3.93 (1H, dd, *J*=12.9, 7.8 Hz); ^{13}C NMR: δ 17.4, 22.9, 36.8, 59.6, 60.0, 60.5, 207.5; HRMS (FAB): *m*/*z* calcd for $C_7H_{11}O_3$, 143.0708; found, 143.0702 ($[M+H]^+$).

*4.1.2. Determination of the enantiomeric excess of **4**.* The enantiomeric excess of **4** was determined to be 92% by analyzing the ^{1}H NMR spectra of the (*R*)-and (*S*)-MTPA esters derived form **4**. The hydroxyl-bearing methylene protons of the (*R*)-MTPA ester appeared at δ 4.61 ppm (1H, d, *J*=12.2 Hz) and δ 4.75 ppm (1H d, *J*=12.2 Hz) as the major peaks (96% in total) and at δ 4.68 ppm (1H, d, *J*=12.7 Hz) and δ 4.70 ppm (1H, d, *J*=12.7 Hz) as the minor peaks (4% in total). These assignments were confirmed by the ^{1}H NMR of the (*S*)-MTPA ester.

*4.1.3. Methyl (1S,6S)-2-oxo-7-oxabicyclo[4.1.0]heptane-1-carboxylate (**3**).* To a stirred solution of **4** (383 mg, 2.70 mmol) in acetone (40 mL) was added dropwise a solution of Jones reagent (2.70 mL, 7.21 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for an additional 2.5 h. The mixture was quenched with *i*-PrOH and concentrated in vacuo. The residue was diluted with water and extracted with EtOAc. The extract was successively washed with water and brine, dried ($MgSO_4$), and

concentrated in vacuo to give **6** as a yellow oil, which was then dissolved in Et_2O (10 mL). To the solution was added dropwise a freshly prepared solution of CH_2N_2 in Et_2O at 0 °C until the gas evolution ceased. The resulting mixture was quenched with AcOH and concentrated in vacuo. The residue was purified by silica gel column chromatography (toluene/EtOAc=30:1) to give 328 mg (71%) of **3** as a white solid. Mp 55.5–56.0 °C; $[\alpha]_D^{23}$ −115 (*c* 1.25, $CHCl_3$); IR: ν_{max} 1753 (s), 1707 (s), 1227 (s), 1061 (s), 770 (m); ^{1}H NMR: δ 1.71–1.91 (2H, m), 2.04 (1H, dddd, *J*=15.4, 11.0, 5.5, 1.4 Hz), 2.17 (1H, ddd, *J*=17.1, 11.7, 5.8 Hz), 2.35 (1H, dm, *J*=15.4 Hz), 2.57 (1H, dt, *J*=17.1, 4.3 Hz), 3.69–3.70 (1H, br m), 3.83 (3H, s); ^{13}C NMR: δ 16.4, 22.8, 37.2, 52.8, 58.6, 60.0, 166.5, 199.3; HRMS (FAB): *m*/*z* calcd for $C_8H_{11}O_4$, 171.0657; found, 171.0657 ($[M+H]^+$).

*4.1.4. Methyl (1R,2S,6S)-2-hydroxy-7-oxabicyclo[4.1.0]heptane-1-carboxylate (**11β**).* To a stirred solution of **3** (827 mg, 4.86 mmol) in THF (40 mL) was added dropwise a solution of L-Selectride® (1.0 M in THF, 5.0 mL, 5.0 mmol) at −78 °C. After 1 h, the mixture was quenched with satd NH_4Cl aq and extracted with EtOAc. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=5:1–1:2) to give 693 mg (83%) of **11β** as a colorless oil and 137 mg (16%) of **11α** as a white solid. Compound **11β**: $[\alpha]_D^{22}$ −71.5 (*c* 1.25, $CHCl_3$); IR: ν_{max} 3618 (br m), 1741 (s), 1265 (s), 1044 (s); ^{1}H NMR: δ 1.25–1.36 (1H, m), 1.56–1.77 (3H, m), 1.87–1.97 (1H, m), 1.99–2.07 (1H, m), 3.59 (1H, dm, *J*=4.3 Hz), 3.63 (1H, br s, OH), 3.79 (3H, s), 4.48 (1H, br s); ^{13}C NMR: δ 13.3, 22.4, 26.1, 52.7, 57.3, 58.6, 64.6, 172.2; HRMS (FAB): *m*/*z* calcd for $C_8H_{13}O_4$, 173.0814; found, 173.0818 ($[M+H]^+$). Compound **11α**: mp 55.0–56.0 °C; $[\alpha]_D^{24}$ −48.8 (*c* 1.23, $CHCl_3$); IR: ν_{max} 3488 (m), 1742 (s), 1255 (s), 1039 (s), 938 (m), 735 (m); ^{1}H NMR: δ 1.25–1.38 (1H, m), 1.45–1.63 (2H, m), 1.64–1.72 (1H, m), 1.82–1.97 (2H, m), 2.28–2.35 (1H, br m, OH), 3.55 (1H, br d, *J*=3.3 Hz), 3.80 (3H, s), 4.58–4.66 (1H, br m); ^{13}C NMR: δ 17.8, 22.9, 28.2, 52.7, 59.9, 61.0, 66.0, 170.6; HRMS (FAB): *m*/*z* calcd for $C_8H_{13}O_4$, 173.0814; found, 173.0818 ($[M+H]^+$).

*4.1.5. Methyl (1S,2S,6S)-2-(tert-butyldimethylsilyloxy)-7-oxabicyclo[4.1.0]heptane-1-carboxylate (**12β**).* To a stirred solution of **11β** (1.30 g, 7.58 mmol) in CH_2Cl_2 (40 mL) was successively added Et_3N (1.60 mL, 11.5 mmol) and TBSOTf (2.20 mL, 9.39 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. The mixture was quenched with satd NH_4Cl aq and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=100:1–25:1) to give 2.07 g (96%) of **12β** as a colorless oil. $[\alpha]_D^{24}$ +7.87 (*c* 1.15, MeOH); IR: ν_{max} 3008 (w), 1746 (vs), 1256 (s), 833 (s); ^{1}H NMR: δ 0.076 (3H, s), 0.092 (3H, s), 0.87 (9H, s), 1.21–1.30 (1H, m), 1.39–1.47 (1H, m), 1.57–1.74 (2H, m), 1.85–2.02 (2H, m), 3.65 (1H, br d, *J*=3.7 Hz), 3.74 (3H, s), 4.45 (1H, br dd, *J*=4.7, 3.7 Hz); ^{13}C NMR: δ −5.2, −4.6, 13.7, 17.9, 22.7, 25.6 (3C), 28.2, 52.1, 57.7, 60.3, 66.0, 169.5; HRMS (FAB): *m*/*z* calcd for $C_{14}H_{27}O_4Si$, 287.1679; found, 287.1676 ($[M+H]^+$).

*4.1.6. Methyl (1S,6S)-6-(tert-butyldimethylsilyloxy)-1-hydroxy-2-cyclohexene-1-carboxylic acid (**14β**).* To a stirred suspension of PhSe-SePh (502 mg, 1.54 mmol) in EtOH (6 mL) was added portionwise $NaBH_4$ (138 mg, 3.34 mmol) at room temperature. After 30 min, a solution of **12β** (575 mg, 2.01 mmol) in EtOH (4 mL) was added, and the resulting mixture was stirred for 8 h. The mixture was cooled to 0 °C and diluted with EtOH (5 mL) and water (5 mL). $NaHCO_3$ (1.10 g, 13.0 mmol) and $NaIO_4$ (2.39 g, 11.2 mmol) was then added, and the resulting mixture was stirred at room temperature for 1 h and then at 60 °C for an additional 3 h. The mixture was diluted with water and extracted with Et_2O. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=20:1) to give 513 mg (89%) of **14β** as a pale yellow oil. $[\alpha]_D^{22}$ −130 (*c* 1.14, $CHCl_3$); IR: ν_{max} 3512 (w), 3032 (w), 1731 (s), 1095 (s), 776 (m); ^{1}H NMR: δ 0.056 (3H, s), 0.077 (3H, s), 0.86 (9H, s), 1.75–1.84 (1H, m), 2.07–2.16 (1H, m), 2.17–2.29 (2H, m), 3.77 (1H, s, OH), 3.79 (3H, s), 4.45 (1H, dd, *J*=11.1, 4.5 Hz), 5.45 (1H, ddd, *J*=9.9, 2.3, 1.7 Hz), 5.94 (1H, ddd, *J*=9.9, 4.7, 2.8 Hz); ^{13}C NMR: δ −4.9, −4.6, 17.8, 23.9, 25.6 (3C), 28.3, 52.8, 75.4, 77.6, 126.3, 131.7, 174.2; HRMS (FAB): *m*/*z* calcd for $C_{14}H_{27}O_4Si$, 287.1679; found, 287.1682 ($[M+H]^+$).

*4.1.7. Methyl (S)-1-hydroxy-6-oxo-2-cyclohexene-1-carboxylate (**2**).* To a stirred solution of **14β** (376 mg, 1.42 mmol) in MeCN (2 mL) was added dropwise a solution of HF (48% aq solution, 1.0 mL) at room temperature. After 45 min, the mixture was quenched with $NaHCO_3$ and stirred for 1 h. The resulting mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give **15β** (229 mg) as a yellow oil, which was then dissolved in CH_2Cl_2 (6 mL). To the solution was successively added $NaHCO_3$ (342 mg, 4.07 mmol) and Dess/Martin periodinane (851 mg, 2.01 mmol) at room temperature. The mixture was stirred for 45 min, quenched with half satd $Na_2S_2O_3$ aq, and then extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=2:1) to give 183 mg (76%) of **2** as a colorless oil. $[\alpha]_D^{24}$ −252 (*c* 1.16, $CHCl_3$) (lit.[7] $[\alpha]_D^{27}$ −274.8 (*c* 1.01, $CHCl_3$)); IR: ν_{max} 3616 (m), 3039 (w), 1746 (s), 1720 (vs), 1136 (m); ^{1}H NMR: δ 2.52–2.63 (1H, m), 2.64–2.79 (2H, m), 3.00 (1H, dt, *J*=14.3, 8.0 Hz), 3.80 (3H, s), 4.26 (1H, s, OH), 5.79 (1H, ddd, *J*=9.8, 2.1, 1.7 Hz), 6.13 (1H, ddd, *J*=9.8, 4.1, 3.9 Hz); ^{13}C NMR: δ 26.8, 35.1, 53.4, 77.9, 127.5, 131.8, 170.3, 205.4; HRMS (EI): *m*/*z* calcd for $C_8H_{10}O_4$, 170.0579; found, 170.0579 (M^+).

*4.1.8. Dimethyl (1′R,2′S,3aS,7aR)-3a,6,7,7a-tetrahydro-2′,7a-dihydroxyspiro[1,3-benzodioxole-2,1′-[3]cyclohexene]-2′,3a-dicarboxylate [Idesolide (**1**)].* A mixture of **2** (20.5 mg, 0.121 mmol) and $NaHCO_3$ powder (20.5 mg, 0.244 mmol) was stirred at room temperature for 8 h and then left to stand for an additional 12 h at the same temperature. The mixture was diluted with $CHCl_3$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography [Merck, silica gel 60 (spherical), 40–50 μm; hexane/EtOAc=2:1] to give 12.2 mg (60%) of **1** as a colorless solid. Mp: 139.5–141.0 °C (lit.[1] mp 141.0–143.0 °C; lit.[7] mp 138–140 °C); $[\alpha]_D^{25}$ −248 (*c* 1.06, $CHCl_3$) [lit.[1] $[\alpha]_D^{25}$ −230.0 (*c* 1.0, $CHCl_3$); lit.[7] $[\alpha]_D^{25}$ −238.9 (*c* 0.27, $CHCl_3$)]; IR: ν_{max} 3411 (w), 3370 (w), 1761 (s), 1728 (s), 1251 (s), 1095 (s), 1075 (s), 800 (m); ^{1}H NMR: δ 1.80–1.88 (1H, m), 2.08–2.47 (7H, m), 3.77 (3H, s), 3.91 (3H, s), 4.86 (1H, br s, OH), 5.46 (1H, ddd, *J*=10.2, 2.4, 1.5 Hz), 5.59 (1H, ddd, *J*=10.2, 2.4, 1.2 Hz), 5.96–6.02 (2H, m), 6.00 (1H, s, OH); ^{13}C NMR: δ 22.4, 24.3, 29.7, 31.0, 52.7, 54.2, 76.6, 86.4, 102.1, 110.9, 126.1, 126.4, 130.6, 132.4, 169.0, 173.1; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{21}O_4$, 341.1236; found, 341.1241 ($[M+H]^+$).

*4.1.9. Methyl (1S,2R)-1,2-dihydroxycyclohexane-1-carboxylate (**16**).* This known compound showed the following properties: colorless oil; $[\alpha]_D^{23}$ +3.55 (*c* 1.30, 95% EtOH) (lit.[22] $[\alpha]_D^{24}$ +2.5 (*c* 1.1, 95% EtOH)); IR: ν_{max} 3470 (br s), 1730 (s), 1238 (s), 1148 (m); ^{1}H NMR: δ 1.25–1.38 (1H, m), 1.48–1.61 (3H, m), 1.65–1.87 (4H, m), 2.23 (1H, br s, OH), 3.40 (1H, br s, OH), 3.80–3.86 (1H, m), 3.82 (3H, s); ^{13}C NMR: δ 19.8, 24.0, 30.2, 34.3, 53.0, 72.2, 76.8, 176.6; HRMS (FAB): *m*/*z* calcd for $C_8H_{15}O_4$, 175.0970; found, 175.0976 ($[M+H]^+$).

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Supplementary data

Supplementary data for this article (^{1}H and ^{13}C NMR spectra of compounds **4**, **6**, **3**, **11β**, **11α**, **12β**, **14β**, **15β**, **2**, and **1**) can be found. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.034. These data include MOL files and InChiKeys of the most important compounds described in this article.

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26. Prolonging the reaction time from 20 h to 2 days as well as increasing the amount of $NaHCO_3$ from 2 equiv to 4 equiv did not improve the chemical yield further.