Toward a Total Synthesis of Okilactomycin. 2. A Metathesis-Based Approach to the Heavily Functionalized Cyclohexane Ring

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Abstract: An attempt to access in an enantioselective fashion, a highly substituted cyclohexane as required for the northeastern sector of okilactomycin is described. The application of Oppolzer's sultam chemistry, involving in particular an optically and chemically efficient asymmetric conjugate addition of a functionalized allylic Grignard reagent in tandem with ring closing metathesis forms the basis of a direct, highly stereocontrolled route to the cyclohexenylmethanol **10**. Ensuing Sharpless epoxidation very efficiently leads to construction of epoxide **11**. This intermediate and its benzyl ether were found to undergo regiocontrolled oxirane ring cleavage with cyanide and chloride ions. However, this precedence was not matched when alternative carbon nucleophiles (particularly allyl) were brought into play. Under no circumstances was a desired product detected. The all-equatorial array of substituents on the cyclohexane is likely responsible for the lack of reactivity toward organometallic reagents.

Key words: metathesis, sultams, cyanation, carbocupration, epoxide, asymmetric conjugate addition

In the preceding article,[1] a retrosynthetic analysis of okilactomycin was outlined in which the coupling of an aldehyde to a highly functionalized cyclohexane related to **1** was defined. Herein, we report an approach to **2** (Scheme 1), which employs an asymmetric conjugate addition plus a ring-closure metathesis reaction and demonstrate the limited reactivity profile of its oxirane ring.
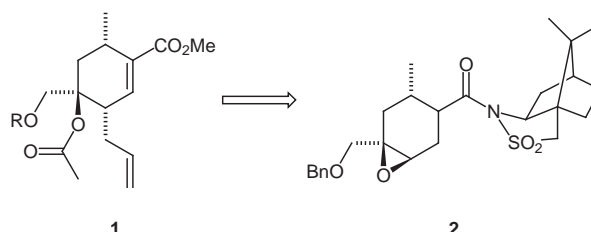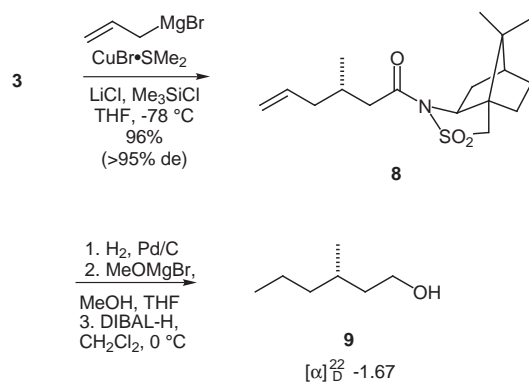

Scheme 1

The pathway to **2** began by capitalizing on the ability of enoyl sultam **3** to enter into conjugate addition reactions with high diastereoselectivity.[2,3] However, the envisioned pathway to **2** required that a functionalized allylic reagent participate in 1,4-conjugate addition to the sultam, a reaction that has not been demonstrated with much success. The functionalized Grignard reagent **4** planned as the reaction partner proved expectedly to be an ill-behaved species. Notwithstanding, adaptation of those conditions recently uncovered by Lipshutz[4] caused the conversion to **5** to be exceptionally workable (Scheme 2). Only when CuBr·SMe₂, lithium chloride, *and chlorotrimethylsilane* are present in combination with 1.2 equivalents of **4** was **5** produced efficiently (98% yield, >95% de). For several reasons, confirmation of the stereochemical course of the
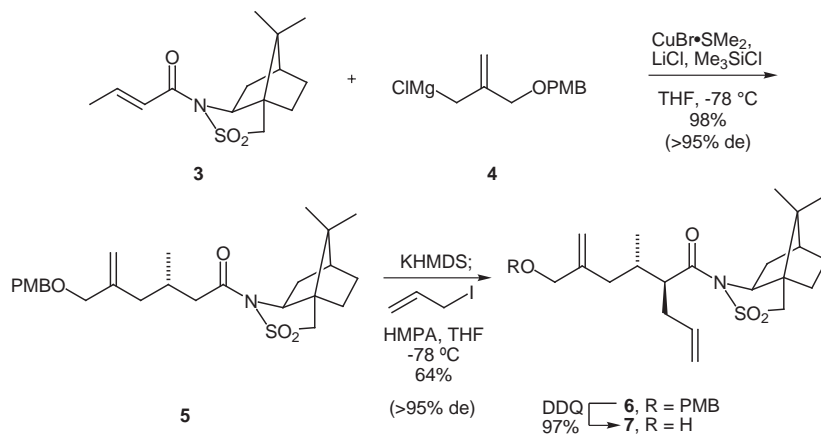
Scheme 2

conjugate addition reaction was considered advisable. For example, the 1,4-addition of simple alkyl Grignard reagents to chiral enoylsultams in the presence[3] or absence[2] of a catalytic amount of copper salt has been shown to afford opposite diastereomers. Also, related reactions involving phosphine-stabilized organocopper species occur with opposite face stereodifferentiation when mediated by $BF_3 \cdot OEt_2$ or $EtAlCl_2$.[5] In the present instance, stereochemical proof was gained by adding allylmagnesium bromide to **3** under totally analogous conditions. As before, the yield of **8** was nearly quantitative and the de was excellent (>95%) (Scheme 3). Following the catalytic hy-

drogenation of **8**, the chiral auxiliary was replaced by means of methoxymagnesium bromide,[6] and the resulting methyl ester was reduced with DIBAL-H at 0 °C. The $[\alpha]_D^{22}$ of alcohol **9** was determined to be −1.67 in $CHCl_3$,[7] and must therefore be the *S* enantiomer[8] as required for okilactomycin.

Acylated camphorsultams have also been shown to be useful chiral auxiliaries for stereoselective α-alkylation, although competitive C−C bond formation involving the activated methylene group adjacent to the sulfonamide functionality has been noted.[9] After considerable experimentation, it was found that the enolization of **5** with 1.05 equivalents of KHMDS in THF at −78 °C followed by addition of a solution of allyl iodide in THF/HMPA at this temperature gave rise to **6** in an optimized 64% yield. The high diastereomeric purity of **6** (>95% ee) is likely due to the cooperative contributions arising from the two chiral components resident in **5**.

With **6** in hand, attention was focused on building of the six-membered cycle via ring closing metathesis.[10] For reasons of economy of catalyst, the feasibility of removing the PMB group first was investigated, notwithstanding our awareness of the problems that allylic hydroxyls can sometimes bring on in the presence of a ruthenium catalyst.[11] Fortunately in this instance, only the activating effect of the OH group[10b,11,12] manifested itself. Indeed, as shown in Scheme 4, stirring **7** with only 0.75 mol percent of the Grubbs catalyst in CH_2Cl_2 at 20 °C led very conve-
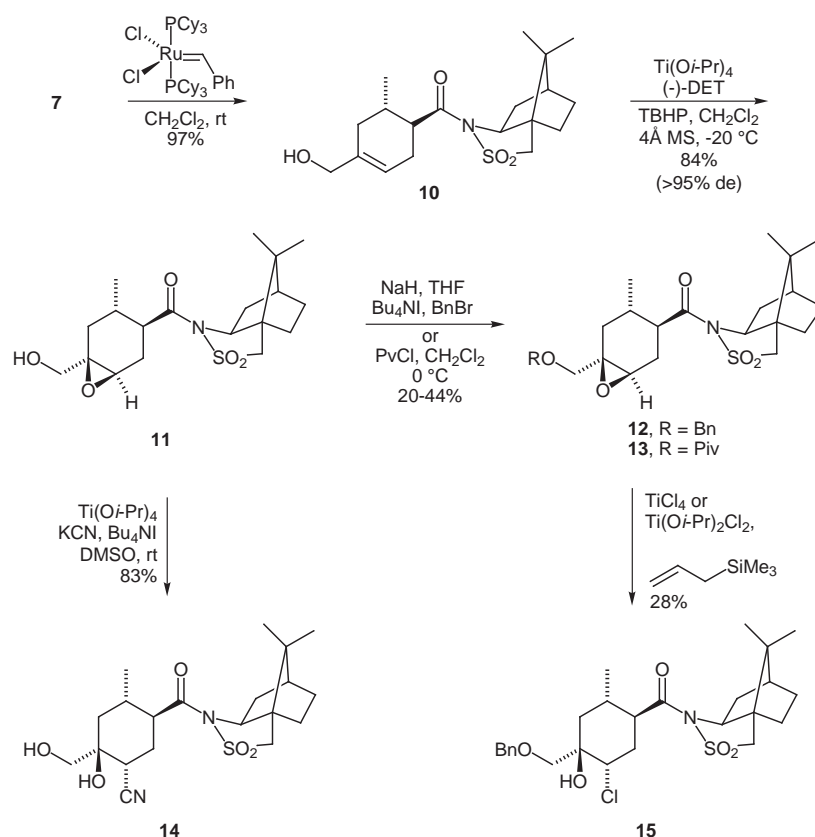
Scheme 3

Scheme 4

niently to **10** in 97% isolated yield. Cyclohexenyl alcohols similar to **10** have been successfully epoxidized under Sharpless conditions with acceptable selectivities.[13] In line with this precedent, the use of (−)-diethyl tartrate afforded the desired epoxide **11**. The diastereomeric bias was very high (>95% de), with only one epoxy alcohol in evidence upon high-field ¹H NMR analysis. The feature that all of the ring substituents in **11** are equatorial likely contributes to the exceptionally high stereoselectivity observed in this step.

The aldehyde obtained from **11** by tetrabutylammonium perruthenate oxidation proved to be a very unstable substance, decomposing readily under mild conditions including the Noyori protocol for acetalization with 1,2-bis(trimethylsiloxy)ethane at −78 °C.[14] As a consequence, our focus was redirected to deferral of this oxidative step to a later stage.

The opening of cyclohexane epoxides is generally recognized to be a difficult process due to unfavorable stereoalignment issues, although many successful examples have been reported. Notwithstanding, **11** and its protected derivatives **12** and **13** proved to be totally resistant to the action of such reagents as allylCu(CN)Li₂, allylMgBr/Cu-Br·SMe₂/BF₃·OEt₂, allylSnBu₃/Ti(i-PrO)₄, allylSiMe₃/Ti(i-PrO)₄, allylMn(Me)₂Li, allylTi(i-PrO)₃ and the like. When recourse was made to allylSiMe₃ in the presence of TiCl₄ or Ti(i-PrO)₂Cl₂, **12** was transformed in modest yield into the chlorohydrin **15**, the chloride ion from the Lewis acid serving as the nucleophile. A still more successful transformation involved the conversion of **11** into **14** (83%) upon exposure of the epoxy alcohol to Ti(i-PrO)₄, KCN, and BuN⁺I⁻ in DMSO at room temperature.[15]

Our hope to introduce the required allyl substituent ultimately rested on the allyldimethylsilyl ether **16**, whose role was to enter into intramolecular allyl transfer in the presence of TiCl₄[16] (see **17**, Scheme 5). However, this extension of Reetz's work proved unsuccessful as well. These insights revealed that the usual explanations advanced for the unreactive topology of cyclohexene oxides are valid for the systems specifically substituted as in **11**–**13**. In the final analysis, the susceptibility of **11** and **12** to nucleophilic oxirane ring opening by chloride and cyanide ion cannot be exploited for alkenyl C−C bond formation. Alternative routes to **1** obviously require development. Their development is currently in progress.

Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230−400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be approximately >95% by TLC and high field ¹H and ¹³C NMR spectroscopy. The high-resolution mass spectra were obtained at the Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at Atlantic Microlab, Inc., Norcorss, GA.

2-(Chloromethyl)-3-*p*-(methoxybenzyloxy)propene
A stirred suspension of anhyd, oil-free NaH (10.0 g, 417 mmol) in anhyd THF (300 mL) was treated dropwise with a soln of 4-methoxybenzyl alcohol (44.24 g, 320 mmol) in anhyd THF (70 mL). Anhyd DMF (80 mL) was added and the reaction mixture was stirred
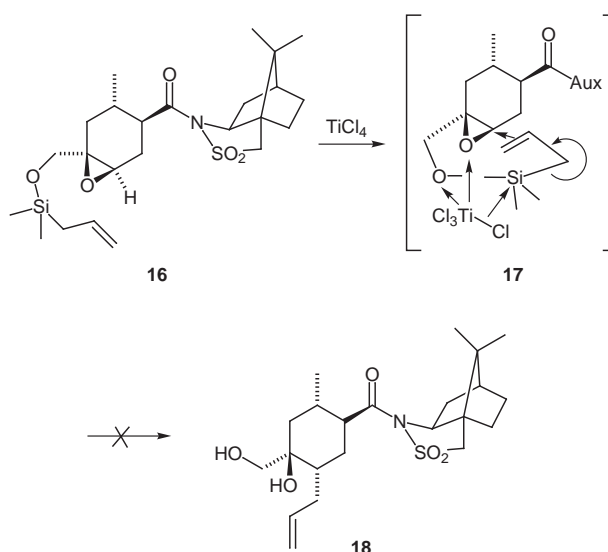
Scheme 5

at r.t. for 30 min, heated at reflux for 1 h, cooled to r.t., and poured into a pressure-equalizing dropping funnel. The reaction flask was rinsed with anhyd THF (50 mL). This mixture was added dropwise over 90 min to a stirred soln of 3-chloro-2-(chloromethyl)-1-propene (65.01 g, 520 mmol) in anhyd THF (400 mL). The dropping funnel was rinsed with anhyd THF (50 mL). The reaction mixture was stirred at r.t. overnight and then poured into a separatory funnel containing Et₂O (250 mL), hexanes (250 mL), brine (500 mL), and H₂O (500 mL). The separated aq layer was extracted with Et₂O−hexanes, 1:1. The combined organic extracts were washed with H₂O, dried, and concentrated under reduced pressure, and purified by flash chromatography (EtOAc−hexanes, 7:93) to afford 54.33 g (75%) of the monoether as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃): δ = 3.81 (s, 3 H), 4.09 (br s, 2 H), 4.13 (br s, 2 H), 4.46 (br s, 2 H), 5.26 (br s, 1 H), 5.32 (br s, 1 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 7.28 (d, *J* = 8.6 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 45.2, 55.2, 70.0, 72.0, 113.8 (2 × C), 116.7, 129.3 (2 × C), 130.1, 142.1, 159.3.

HRMS (EI): *m/z* calcd for C₁₂H₁₅ClO₂ (M⁺), 226.0761; found, 226.0768.

Acylsultam 5
To a mechanically stirred suspension of freshly ground magnesium turnings (58.22 g, 2.39 mol) in anhyd, degassed THF (900 mL) was added 1,2-dibromoethane (5.2 mL, 0.060 mol) via syringe. (The anhyd THF was degassed by repeated cycles of exposing the anhyd solvent to house vacuum during sonication and subsequent purging with argon). After a slight induction period (1−3 min), evolution of gas was observed and the reaction was slightly exothermic. The reaction mixture was stirred at r.t. for 30 min and a soln of the allylic chloride (54.3 g, 0.240 mol) in anhyd, degassed THF (225 mL) was introduced dropwise during 5.5 h. After an additional 1.5 h, the stirrer was removed, the flask was stoppered and stored in the freezer (~ −5 °C) overnight to give a gray-colored soln of **4** in a total volume of 1105 mL of THF. Titration established the concentration to be 0.12 M (55%).[17]

A suspension of CuBr·Me₂S (30.52 g, 148.5 mmol) and anhyd LiCl (6.78 g, 160 mmol) in anhyd THF (250 mL) was stirred at r.t. for 15−20 min and added via cannula to a cold (−78 °C) stirred soln of **4**[18] (1100 mL, 0.12 M in THF, 132 mmol) from above. The reaction flask was rinsed with anhyd THF (10 mL). To the reaction mixture

was added TMSCl (19 mL, 150 mmol) followed by a soln of **3** (32.36 g, 114 mmol) in anhyd THF (260 mL) via an addition funnel. The funnel was rinsed with anhyd THF (30 mL). The reaction mixture was stirred at –78 °C for 90 min, diluted with aq NH$_4$Cl-NH$_4$OH (pH 8–9, 200 mL), warmed to r.t., and stirred until the aq layer was a deep blue color. Et$_2$O and H$_2$O were added, the separated aq layer was extracted with Et$_2$O, the combined organic extracts were washed successively with H$_2$O and brine, dried, and concentrated. The residue consisted of only one diastereomer as indicated by high field ^{1}H NMR (> 95% de). To the crude oil thus obtained was added MeOH (50 mL) hexanes (100 mL), and the soln was stored in the freezer (~ –5 °C) overnight to afford colorless crystals. The crystals were filtered and the mother liquor was concentrated in advance of flash chromatography (EtOAc–hexanes, 2:8). There was isolated a total of 53.48 g (98%) of **5** as colorless crystals; mp 53.5–55 °C.

$[\alpha]_D^{22}$ +68.6 (*c* 3.4, CHCl$_3$).

IR (neat): 1694, 1612, 1513, 1455, 1329 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.952 (d, *J* = 6.5 Hz, 3 H), 0.954 (s, 3 H), 1.13 (s, 3 H), 1.22–1.42 (m, 3 H), 1.81–1.92 (m, 2 H), 1.98–2.12 (m, 4 H), 2.28–2.38 (m, 1 H), 2.49 (dd, *J* = 16.1, 7.6 Hz, 1 H), 2.75 (dd, *J* = 16.1, 5.8 Hz, 1 H), 3.44 (AB$_q$, *J*$_{AB}$ = 13.8 Hz, υ$_{AB}$ = 27.4 Hz, 2 H), 3.80 (s, 3 H), 3.86 (dd, *J* = 6.6, 6.6 Hz, 1 H), 3.92 (AB$_q$, *J*$_{AB}$ = 12.8 Hz, υ$_{AB}$ = 14.8 Hz, 2 H), 4.42 (AB$_q$, *J*$_{AB}$ = 11.5 Hz, υ$_{AB}$ = 8.6 Hz, 2 H), 4.94 (br s, 1 H), 5.09 (br s, 1 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.27 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 19.6, 20.8, 26.5, 28.0, 32.8, 38.5, 40.8, 42.8, 44.7, 47.7, 48.3, 53.0, 55.2, 65.2, 71.7, 72.4, 113.6, 113.7 (2 C), 129.2 (2 C), 130.6, 144.0, 159.1, 171.3 (one signal not observed).

HRMS (EI): *m/z* calcd for C$_{26}$H$_{38}$NO$_5$S (M + 1)$^+$, 476.2471; found, 476.2367.

Anal. Calcd for C$_{26}$H$_{37}$NO$_5$S (475.64): C, 65.66; H, 7.84. Found: C, 65.37; H, 7.86.

Allylation of 5

To a cold (–78 °C) stirred soln of **5** (47.37 g, 99.6 mmol) in anhyd THF (500 mL) was added KHMDS (218 mL, 0.48 M in toluene, 104.6 mmol) dropwise over 20 min. The reaction mixture was stirred at –78 °C for 1.5 h, a soln of allyl iodide (50.19 g, 299 mmol) and anhyd HMPA (52.0 mL, 299 mmol) in anhyd THF (150 mL) was added over 10 min, and the reaction mixture was stirred at –78 °C for 70 min before dilution with H$_2$O (200 mL), brine (200 mL) and warming to r.t. Et$_2$O was added and the separated aq layer was extracted with Et$_2$O. The combined organic extracts were washed with H$_2$O, dried, and concentrated under reduced pressure. The residue consisted of only one diastereomer as indicated by high field ^{1}H NMR (> 95% de). Purification by flash chromatography (EtOAc–hexanes, 2:8) afforded **6** (33.18 g, 64%) as a colorless solid; mp 92–93 °C.

$[\alpha]_D^{22}$ +54.3 (*c* 3.1, CHCl$_3$).

IR (neat): 1680, 1649, 1613, 1586, 1513 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.93 (d, *J* = 6.6 Hz, 3 H), 0.96 (s, 3 H), 1.16 (s, 3 H), 1.24–1.48 (m, 2 H), 1.76 (dd, *J* = 13.8, 11.4 Hz, 1 H), 1.82–1.93 (m, 3 H), 2.01–2.16 (m, 3 H), 2.34–2.57 (m, 3 H), 3.01 (ddd, *J* = 8.3, 8.3, 4.6 Hz, 1 H), 3.45 (AB$_q$, *J*$_{AB}$ = 16.9 Hz, υ$_{AB}$ = 24.9 Hz, 2 H), 3.80 (s, 3 H), 3.82–3.96 (m, 1 H), 3.90 (AB$_q$, *J*$_{AB}$ = 11.5 Hz, υ$_{AB}$ = 8.6 Hz, 2 H), 4.42 (AB$_q$, *J*$_{AB}$ = 11.9 Hz, υ$_{AB}$ = 20.2 Hz, 2 H), 4.93 (br s, 1 H), 4.96 (dd, *J* = 10.2, 0.7 Hz, 1 H), 5.04 (dd, *J* = 17.0, 1.0 Hz, 1 H), 5.10 (br s, 1 H), 5.73 (m, 1 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.27 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.4, 19.9, 20.8, 26.4, 31.9, 32.9, 35.3, 37.0, 38.5, 44.6, 47.7, 47.9, 50.3, 53.3, 55.2, 65.5, 71.7, 72.5,

113.3, 113.7 (2 C), 117.2, 129.2 (2 C), 130.6, 135.0, 144.2, 159.1, 174.3.

HRMS (EI): *m/z* calcd for C$_{29}$H$_{41}$NO$_5$S (M$^+$), 515.2705; found, 515.2675.

Anal. Calcd for C$_{29}$H$_{41}$NO$_5$S (515.71): C, 67.54; H, 8.01. Found: C, 67.36; H, 8.01.

Deprotection of 6

To a vigorously stirred soln of **6** (20.00 g, 38.64 mmol) in CH$_2$Cl$_2$ (390 mL) and H$_2$O (39 mL) was added DDQ (13.18 g, 58.1 mmol). The reaction mixture turned green immediately and faded to orange over time with the formation of a precipitate. After 45 min, sat. NaHCO$_3$ soln (200 mL) and H$_2$O were added to the reaction mixture, the separated aq layer was extracted with CH$_2$Cl$_2$, and the combined organic extracts were washed with H$_2$O, dried, and concentrated. The residue was recrystallized from MeOH–hexanes with cooling in the freezer. The acquired colorless crystals were filtered and the mother liquor was concentrated and purified by flash chromatography (EtOAc–hexanes, 2:3) to give a total of 14.76 g (97%) of **7** as a colorless solid; mp 108–108.5 °C.

$[\alpha]_D^{22}$ +87.6 (*c* 5.3, CHCl$_3$).

IR (neat): 3490, 1638, 1456, 1393 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.93 (d, *J* = 6.7 Hz, 3 H), 0.95 (s, 3 H), 1.15 (s, 3 H), 1.28–1.45 (m, 2 H), 1.64 (br s, 1 H), 1.75 (dd, *J* = 13.9, 11.1 Hz, 1 H), 1.80–1.94 (m, 3 H), 1.97–2.12 (m, 3 H), 2.36–2.55 (m, 3 H), 3.02 (ddd, *J* = 8.0, 8.0, 5.0 Hz, 1 H), 3.46 (AB$_q$, *J*$_{AB}$ = 13.8 Hz, υ$_{AB}$ = 18.1 Hz, 2 H), 3.90 (dd, *J* = 6.4, 6.4 Hz, 1 H), 4.03 (br s, 2 H), 4.87 (br s, 1 H), 4.98 (dd, *J* = 10.1, 0.8 Hz, 1 H), 5.06 (dd, *J* = 17.1, 1.6 Hz, 1 H), 5.07 (br s, 1 H), 5.73–5.88 (m, 1 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.4, 19.9, 20.8, 26.4, 32.0, 32.9, 35.0, 36.6, 38.5, 44.6, 47.7, 48.0, 50.0, 53.3, 65.5, 65.6, 111.1, 117.3, 134.9, 147.0, 174.4.

HRMS (EI): *m/z* calcd for C$_{21}$H$_{32}$NO$_4$S (M$^+$–1), 394.2052; found, 394.2033.

Anal. Calcd for C$_{21}$H$_{33}$NO$_4$S (394.54): C, 63.93; H, 8.17. Found: C, 63.73; H, 8.29.

Cyclization of 7 by Ring-Closing Metathesis

To a soln of **7** (11.85 g, 30.0 mmol) in anhyd CH$_2$Cl$_2$ (550 mL) was added a soln of the Grubbs' catalyst (183 mg, 0.22 mmol) in anhyd CH$_2$Cl$_2$ (50 mL) via cannula. The soln was stirred at r.t. for 23 h prior to solvent evaporation, and the residue was twice recrystallized from MeOH. The mother liquor was purified by flash chromatography (EtOAc–hexanes, 2:3) to furnish a total of (10.73 g, 97%) of **10** as a colorless solid: m.p. 209–211 °C.

$[\alpha]_D^{22}$ +158 (*c* 3.5, CHCl$_3$).

IR (neat): 3302, 1681, 1400, 1326 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.96 (s, 3 H), 1.00 (d, *J* = 6.2 Hz, 3 H), 1.13 (s, 3 H), 1.28–1.46 (m, 2 H), 1.54 (br s, 1 H), 1.72–1.93 (m, 4 H), 2.01–2.22 (m, 5 H), 2.44 (br d, *J* = 16.7 Hz, 1 H), 2.89 (ddd, *J* = 10.7, 10.7, 5.2 Hz, 1 H), 3.47 (AB$_q$, *J*$_{AB}$ = 13.8 Hz, υ$_{AB}$ = 16.8 Hz, 2 H), 3.92 (dd, *J* = 6.2, 6.2 Hz, 1 H), 3.98 (br s, 2 H), 5.63 (br s, 1 H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 19.5, 19.8, 20.8, 26.4, 29.7, 30.6, 32.8, 33.4, 38.5, 44.6, 47.4, 47.7, 48.2, 53.2, 65.0, 66.7, 120.0, 137.4, 175.1.

HRMS (EI): *m/z* calcd for C$_{19}$H$_{29}$NO$_4$S (M$^+$), 367.1817; found, 367.1801.

Anal. Calcd for C$_{19}$H$_{29}$NO$_4$S (367.50): C, 62.10; H, 7.95. Found: C, 61.84; H, 7.84.

Asymmetric Epoxidation of 10

To a cold (–20 °C) stirred soln of (–)-diethyl tartrate (680 mg, 3.30 mmol) in anhyd CH_2Cl_2 (170 mL) containing freshly activated, dried, and crushed 4 Å molecular sieves (13.8 g) was added neat Ti(*i*-PrO)$_4$ (0.81 mL, 2.74 mmol) and stirring was maintained at –20 °C for 20 min. A soln of **10** (10.10 g, 27.5 mmol) in anhyd CH_2Cl_2 (150 mL) was introduced via cannula over 20 min and the mixture was stirred at –20 °C for an additional 20 min. A soln of *tert*-butyl hydroperoxide in CH_2Cl_2 (16.0 mL, 5.3 M in CH_2Cl_2 stored over molecular sieves prior to the addition, 84.8 mmol) was added and the mixture was stirred at –20 °C for 3 h prior to the addition of neat dimethyl sulfide (7.5 mL), stirred at –20 °C for 1 h, warmed to r.t., and filtered to remove the sieves. To the filtrate was added a soln of 11% (w/v) of aq citric acid (160 mL) and the reaction mixture was stirred at r.t. overnight. The separated aq phase was extracted with CH_2Cl_2 and Et_2O. The combined organic extracts were washed with H_2O, dried, and concentrated. The residue consisted of only one diastereomer as indicated by high field ^1H NMR (>95% de). The crude product was recrystallized from MeOH to afford colorless crystals. The mother liquor was concentrated under reduced pressure and purified by flash chromatography (EtOAc–hexanes, 2:3) to furnish a total of 8.82 g (84%) of **11** as a colorless solid; mp 168–170 °C.

$[\alpha]_D^{22}$ +161 (*c* 2.2, CHCl$_3$).

IR (neat): 3300, 1676, 1399, 1326 cm^{-1}.

^1H NMR (300 MHz, CDCl$_3$): δ = 0.91 (d, *J* = 6.3 Hz, 3 H), 0.97 (s, 3 H), 1.14 (s, 3 H), 1.29–1.48 (m, 3 H), 1.73 (br s, 1 H), 1.82–1.95 (m, 4 H), 1.98–2.13 (m, 4 H), 2.38 (ddd, *J* = 15.1, 5.5, 5.5 Hz, 1 H), 2.66 (ddd, *J* = 11.0, 11.0, 6.4 Hz, 1 H), 3.28 (d, *J* = 5.5 Hz, 1 H), 3.47 (AB$_q$, *J*$_{AB}$ = 14.0 Hz, υ$_{AB}$ = 19.3 Hz, 2 H), 3.59 (br d, *J* = 12.2 Hz, 1 H), 3.72 (br d, *J* = 12.2 Hz, 1 H), 3.89 (br dd, *J* = 6.2, 6.2 Hz, 1 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 19.0, 19.8, 20.8, 26.4, 26.6, 28.7, 32.8, 33.2, 38.4, 44.6, 46.8, 47.7, 48.3, 53.2, 54.3, 61.1, 64.0, 65.0, 174.0.

HRMS (EI): *m/z* calcd for C$_{19}$H$_{29}$NO$_5$S (M$^+$), 383.1766; found, 383.1775.

Anal. Calcd for C$_{19}$H$_{29}$NO$_5$S (383.50): C, 59.51; H, 7.62. Found: C, 59.79; H, 7.68.

O-Benzylation of 11

To a cold (0 °C) stirred soln of **11** (295 mg, 0.77 mmol) in anhyd THF (7.5 mL) was added anhyd oil-free NaH (28 mg, 0.84 mmol). The reaction mixture was stirred at 0 °C

for 10 min, at which point benzyl bromide (125 μL, 1.15 mmol) and tetra-*N*-butylammonium iodide (140 mg, 0.38 mmol) were introduced and the temperature was allowed to rise to 20 °C. H_2O was added, the separated aq layer was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. The residue was purified by flash chromatography to give 71 mg (20%) of **12** as a colorless solid.

^1H NMR (300 MHz, CDCl$_3$): δ = 0.91 (d, *J* = 6.5 Hz, 3 H), 0.97 (s, 3 H), 1.14 (s, 3 H), 1.22–1.45 (m, 2 H), 1.51 (dd, *J* = 14.8, 11.7 Hz, 1 H), 1.79–2.08 (m, 7 H), 2.19 (dd, *J* = 14.7, 4.3 Hz, 1 H), 2.37 (ddd, *J* = 15, 5.3, 5.3 Hz, 1 H), 2.66 (ddd, *J* = 11.2, 11.2, 6.5 Hz, 1 H), 3.12 (d, *J* = 5.2 Hz, 1 H), 3.43 (d, *J* = 11 Hz, 1 H), 3.46 (AB$_q$, *J*$_{AB}$ = 13.8 Hz, υ$_{AB}$ = 18.0 Hz, 2 H), 3.60 (d, *J* = 11 Hz, 1 H), 3.89 (dd, *J* = 6.2, 6.2 Hz, 1 H), 4.54 (AB$_q$, *J*$_{AB}$ = 12.0 Hz, υ$_{AB}$ = 11.4 Hz, 2 H), 7.26–7.40 (m, 5 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 19.0, 19.8, 20.8, 26.39, 26.42, 28.7, 32.7, 33.5, 38.4, 44.6, 46.7, 47.7, 48.2, 53.2, 54.5, 60.0, 65.0, 73.2, 73.3, 127.7 (2 × C), 128.4 (3 × C), 138.0, 174.1.

HRMS (EI): *m/z* calcd for C$_{26}$H$_{35}$NO$_5$S (M$^+$), 473.2236; found, 473.2236.

Pivalate Ester 13

To a cold (0 °C) stirred soln of **11** (210 mg, 0.55 mmol) in anhyd CH_2Cl_2 (5 mL) was added pivaloyl chloride (104 μmol, 0.844 mmol) and pyridine (70 μL, 0.865 mmol). The reaction mixture was stirred at 0 °C for 1 h and warmed to r.t. for 18 h. H_2O was added, the separated aq layer was extracted with CH_2Cl_2, the combined organic extracts were washed with H_2O, dried, and concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 2:8) to afford **13** as a colorless solid (113 mg, 44%).

^1H NMR (300 MHz, CDCl$_3$): δ = 0.87 (d, *J* = 6.5 Hz, 3 H), 0.94 (s, 3 H), 1.10 (s, 3 H), 1.18 (s, 9 H), 1.27 (m, 2 H), 1.42 (dd, *J* = 14.6, 11.7 Hz, 1 H), 1.75–2.05 (m, 7 H), 2.10 (dd, *J* = 14.6, 4.2 Hz, 1 H), 2.35 (ddd, *J* = 15.0, 5.5, 5.5 Hz, 1 H), 2.62 (ddd, *J* = 11.1, 11.1, 6.5 Hz, 1 H), 3.13 (d, *J* = 5.1 Hz, 1 H), 3.44 (AB$_q$, *J*$_{AB}$ = 13.8 Hz, υ$_{AB}$ = 18.9 Hz, 2 H), 3.86 (dd, *J* = 6.4 Hz, 1 H), 3.89 (d, *J* = 12.0 Hz, 1 H), 4.25 (d, *J* = 12.0 Hz, 1 H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 18.9, 19.7, 20.7, 26.29, 26.31, 27.1 (3 × C), 28.5, 32.6, 33.3, 38.3, 38.8, 44.5, 46.4, 47.6, 48.2, 53.1, 54.6, 58.7, 64.9, 66.4, 173.8, 177.8.

HRMS (EI): *m/z* calcd for C$_{24}$H$_{37}$NO$_6$S (M$^+$), 467.2342; found, 467.2354.

Nitrile 14

To a stirred soln of **11** (300 mg, 0.78 mmol), KCN (114 mg, 1.75 mmol), and tetra-*N*-butylammonium iodide (433 mg, 1.17 mmol) in anhyd DMSO (4 mL) at r.t. was added Ti(*i*-PrO)$_4$ (0.51 mL, 1.73 mmol). The reaction mixture was stirred for 12 h, and Et_2O and 5% H_2SO_4 were carefully introduced (CAUTION: HCN is evolved; perform in a well vented hood!). The mixture was stirred vigorously for 30–45 min to give two clear layers, which were separated. The aq layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (EtOAc–hexanes, 7:3). The acquired material was absorbed on silica gel and purified a second time by flash chromatography (EtOAc–hexanes, 7:3) to afford **14** (267 mg, 83%) as a colorless solid.

^1H NMR (400 MHz, CDCl$_3$): δ = 0.96 (d, *J* = 7.5 Hz, 3 H), 0.97 (s, 3 H), 1.15 (s, 3 H), 1.30–1.48 (m, 3 H), 1.61–1.71 (m, 1 H), 1.83–1.99 (m, 3 H), 2.00–2.21 (m, 5 H), 2.30–2.42 (m, 1 H), 2.50 (br s, 1 H), 2.98–3.11 (m, 2 H), 3.48 (AB$_q$, *J*$_{AB}$ = 13.8 Hz, υ$_{AB}$ = 23.3 Hz, 2 H), 3.57 (d, *J* = 11 Hz, 1 H), 3.86 (d, *J* = 11 Hz, 1 H), 3.92 (dd, *J* = 6.2, 6.2 Hz, 1 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 19.6, 19.9, 20.8, 26.4, 27.4, 28.0, 32.8, 33.5, 37.5, 38.4, 44.6, 47.3, 47.8, 48.5, 53.0, 64.9, 68.2, 71.9, 119.0, 173.4.

HRMS (EI): *m/z* calcd for C$_{20}$H$_{31}$N$_2$O$_5$S (M+1)$^+$, 411.1954; found, 411.1981.

Chloro Sultam 15

A soln of **12** (95 mg, 0.20 mmol) in anhyd CH_2Cl_2 (2 mL) was cooled to –78 °C, treated dropwise with TiCl$_4$ (1.0 mL of 1.0 M in CH_2Cl_2, 1.0 mmol), stirred at –78 °C for 1.5 h, and allowed to warm to r.t. After dilution with sat. NH$_4$Cl soln, H_2O, and CH_2Cl_2, the separated aq phase was extracted with CH_2Cl_2, and the combined organic layers were washed with H_2O, dried, and concentrated. Flash chromatographic purification of the residue (EtOAc–hexanes, 2:8) furnished 29 mg (28%) of **15** as a colorless solid.

^1H NMR (300 MHz, CDCl$_3$): δ = 0.92 (d, *J* = 6.5 Hz, 3 H), 0.96 (s, 3 H), 1.14 (s, 3 H), 1.17–1.27 (m, 1 H), 1.28–1.45 (m, 2 H), 1.47–1.55 (m, 2 H), 1.81–1.97 (m, 3 H), 2.00–2.17 (m, 2 H), 2.28–2.46 (m, 2 H), 2.72 (br s, 1 H), 3.13–3.25 (m, 1 H), 3.31 (d, *J* = 11 Hz, 1 H), 3.39–3.52 (m, 2 H), 3.66–3.76 (m, 1 H), 3.90 (m, 1 H), 4.20 (m,

1 H), 4.80 (AB$_q$, J_{AB} = 12.0 Hz, v_{AB} = 11.5 Hz, 2 H), 7.26–7.37 (m, 5 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 19.7, 19.9, 20.9, 26.4, 27.4, 32.8, 33.5, 35.2, 38.5, 44.6, 45.3, 47.7, 48.3, 53.2, 59.1, 65.0, 73.2, 73.6, 74.8, 127.8 (2 × C), 127.9, 128.5 (2 × C), 137.7, 174.5.

HRMS (EI): m/z calcd for C$_{26}$H$_{36}$ClNO$_5$S (M$^+$), 509.2003; found, 509.1993.

Allyl Silyl Ether 16

To a stirred soln of allyldimethylsilyl chloride (97 mg, 0.72 mmol), Et$_3$N (100 μL, 0.72 mmol), and DMAP (14 mg, 0.12 mmol) in anhyd CH$_2$Cl$_2$ (2 mL) at r.t. was added **11** (1.007 g, 2.62 mmol) via cannula as a soln in anhyd CH$_2$Cl$_2$ (3 mL). The reaction mixture was stirred for 4 h, H$_2$O was added, and the separated aq layer was extracted with CH$_2$Cl$_2$. The combined organic extracts were washed with H$_2$O, dried, and concentrated. The residue was purified by flash chromatography (EtOAc−hexanes, 2:8) to afford 229 mg (87%) of **16** as a colorless solid.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.07 (s, 6 H), 0.85 (d, J = 6.4 Hz, 3 H), 0.93 (s, 3 H), 1.09 (s, 3 H), 1.19–1.35 (m, 2 H), 1.40 (dd, J = 14.4, 11.6 Hz, 1 H), 1.58 (d, J = 8.0 Hz, 2 H), 1.73–2.04 (m, 7 H), 2.05 (dd, J = 14.4, 4.3 Hz, 1 H), 2.31 (ddd, J = 15.0, 5, 5 Hz, 1 H), 2.60 (ddd, J = 11.1, 11.1, 6.5 Hz, 1 H), 3.07 (d, J = 5 Hz, 1 H), 3.43 (AB$_q$, J_{AB} = 13.8 Hz, v_{AB} = 18.3 Hz, 2 H), 3.59 (AB$_q$, J_{AB} = 11.5 Hz, v_{AB} = 33.4 Hz, 2 H), 3.84 (dd, J = 6.1, 6.1 Hz, 1 H), 4.77–4.89 (m, 2 H), 5.65–5.81 (m, 1 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = –2.6 (2 × C), 18.9, 19.7, 20.7, 24.2, 26.28, 26.34, 28.7, 32.6, 33.0, 38.3, 44.5, 46.7, 47.6, 48.1, 53.1, 54.5, 60.8, 64.9, 66.0, 113.7, 133.7, 174.0.

HRMS (EI): m/z calcd for C$_{24}$H$_{39}$NO$_5$S SI (M$^+$), 481.2318; found, 481.2322.

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