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Oxabicyclo[3.2.1]octenes in Organic Synthesis: Direct Ring Opening of Oxabicyclo[3.2.1] Ring Systems with Diisobutylaluminum Hydride and a Silyl Ketene Acetal—Synthesis of the Chiral C(19)–C(26) and C(27)–C(32) Fragments of Scytophycin C

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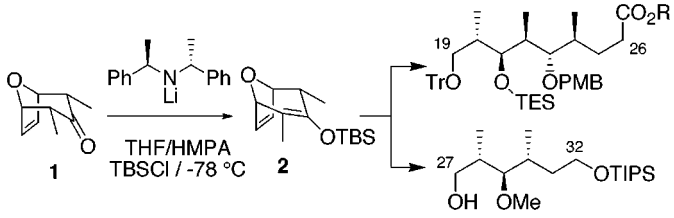
ABSTRACT



An efficient strategy for transforming *meso*-oxabicyclo[3.2.1]octenone 1 into optically active intermediates for macrolide synthesis has been developed. The direct bridgehead opening of optically active oxabicyclo[3.2.1]octene derivative 2 with hydride or a silyl ketene acetal utilizing the highly polar medium lithium perchlorate in diethyl ether resulted in highly functionalized cycloheptenones, which were transformed into the C(19)–C(26) and C(27)–C(32) fragments of Scytophycin C.

We recently disclosed a procedure[1] for the direct bridgehead opening of activated oxabicyclic molecules employing silyl ketene acetals in the highly polar medium 4.0 M lithium perchlorate−diethyl ether (LPDE)[2][eq 1]. We now wish to disclose (1) the desymmetrization of the starting oxabicyclo-[3.2.1]octenone **1** via enantioselective deprotonation [eq 2], (2) the direct bridgehead opening of the oxa bridge of **2** employing diisobutylaluminum hydride[3] leading to the direct formation of cycloheptenone **4** [eq 3], (3) the use of **4** in the construction of the C(27)−C(32) fragment **7** of Scytophycin C (**5**),[4] and (4) the transformation of optically active **3** into the C(19)−C(26) subunit **6** of **5**. In contrast to the use of rigid oxabicyclo[3.2.1]octenes as stereocontrol vehicles for the preparation of the acyclic fragments of **5** as detailed

(1) Hunt, K. W.; Grieco, P. A. *Org. Lett.* **2001**, *3*, 481.

(2) For the use of highly polar media to promote organic reactions, see: Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595. Grieco, P. A. *Aldrichimica Acta* **1991**, *24*, 59. Grieco, P. A. Organic Chemistry in Lithium Perchlorate/Diethyl Ether. In *Organic Chemistry: Its Language and Its State of the Art*; Kisakurek, V., Ed.; VCH: Basel, 1993; p 133.

(3) For the complementary S_N2' opening of oxabicyclo[3.2.1]octenes employing diisobutylaluminum hydride see: Lautens, M.; Chiu, P.; Colucci, J. T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 281.

(4) (a) For the total synthesis of Scytophycin C, see: Paterson, I.; Watson, C.; Kap-Sun, Y.; Wallace, P. A.; Ward, R. A. *J. Org. Chem.* **1997**, *62*, 452. Paterson, I.; Watson, C.; Kap-Sun, Y.; Wallace, P. A.; Ward, R. A. *Tetrahedron* **1998**, *54*, 11935; 11955. (b) For previous synthetic studies, see: Grieco, P. A.; Speake, J. D.; Yeo, S. K.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 1125. Grieco, P. A.; Speake, J. A. *Tetrahedron Lett.* **1998**, *39*, 1275. (c) Roush, W. R.; Dilley, G. J. *Tetrahedron Lett.* **1999**, *40*, 4955.

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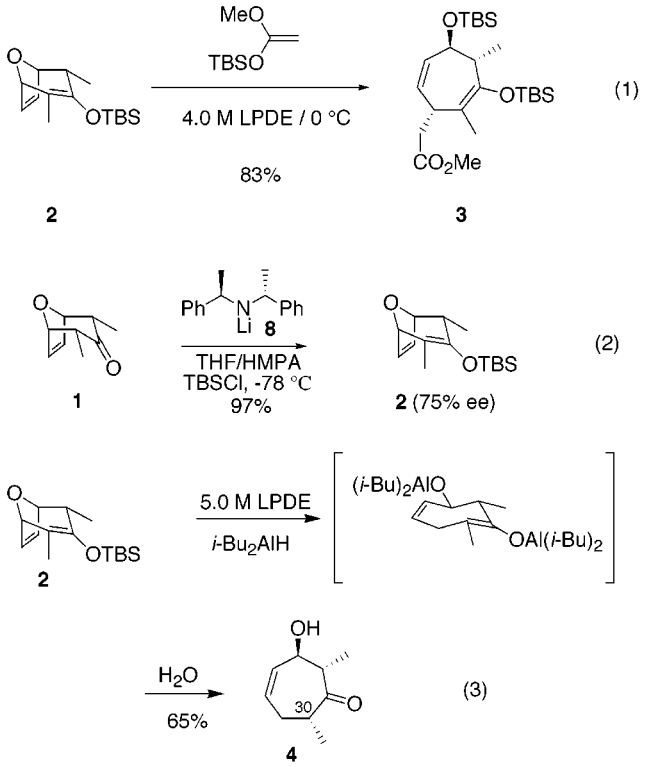
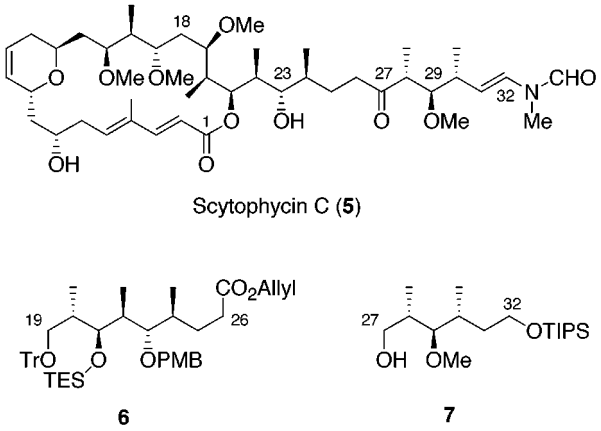


below, previous efforts in this area have employed asymmetric crotylboration,[4] boron-mediated aldol reactions,[4a] methyl ketone aldol reactions,[4a,c] and methylation of γ,δ-epoxy acrylates employing trimethylaluminum.[4b]

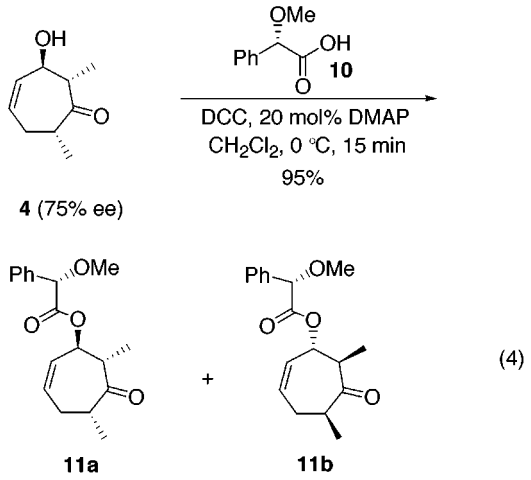


The synthetic studies commenced with desymmetrizing ketone **1** via enantioselective deprotonation.[5] Thus, deprotonation of **1** with the homochiral lithium amide base **8**, derived from [*R*-(*R**,*R**)]-(+)-bis(α-methylbenzyl)amine (**9**), in tetrahydrofuran containing HMPA and *tert*-butyldimethylsilyl chloride (TBSCl) at −78 °C for 24 h provided (97%) optically active enol silane **2**. The enantiomeric purity of the desymmetrized material was found to be 75% ee (vide infra).[6] In contrast to previous work,[7] the use of HMPA and the exclusion of lithium chloride proved crucial to the yield and enantioselectivity of the reaction.

(5) Koga, K. *Pure Appl. Chem.* **1994**, *66*, 1487. Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1.

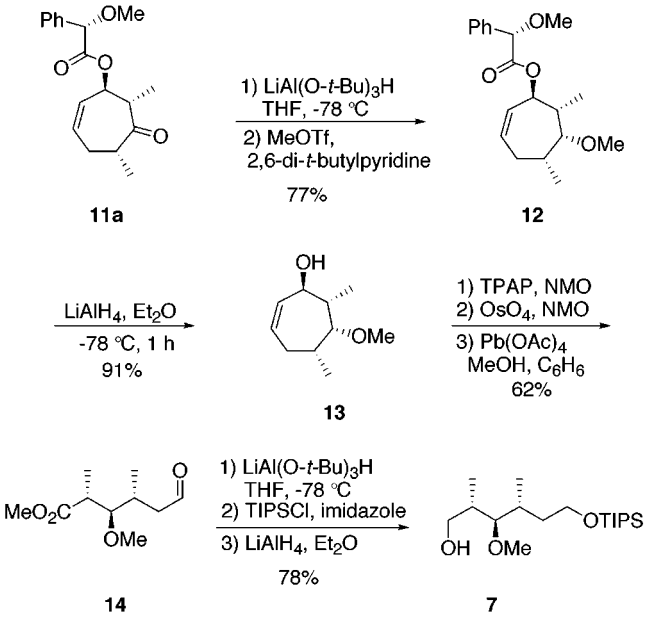
The synthetic strategy for accessing the C(27)−C(32) fragment **7** of Scytophycin C required bridgehead addition of hydride to enol silane **2**. Initially, **2** was treated with a variety of silanes (triethyl, triphenyl, triethoxy, chlorodiphenyl) in concentrated solutions of LPDE (3.0−5.0 M) at ambient temperature.[8] In all cases studied, only recovered starting material was detected by TLC and ^{1}H NMR analysis. Use of traditional Lewis acids (BF_3·OEt_2, $TiCl_4$) resulted in hydrolysis of the enol silane to provide *meso* ketone **1**. Finally, it was found that addition of diisobutylaluminum hydride (DIBALH) to enol silane **2** in 5.0 M LPDE provided the β-hydroxy cycloheptenone **4** in 65% yield (eq 3).[9] The stereochemistry of the eventual stereogenic center at C(30) is a result of an axial-like protonation of the intermediate aluminum enolate (cf. eq 3) upon aqueous workup. It is important to note that exposure of enol silane **2** to 5.0 M LPDE in the absence of DIBALH for 24 h returns **2** without any loss of optical activity.

With the hydride opened product **4** in hand, the stage was set for determining and increasing the enantiomeric excess. Although conversion of **4** into the corresponding Mosher ester[10] clearly revealed by ^{1}H NMR analysis that the enantiopurity of **4** was 75% ee, the resulting diastereomeric esters were not readily separable. After surveying a series of mandelic acid derivatives, it was found that coupling (DCC, cat. DMAP, CH_2Cl_2, 0 °C) of **4** with (*S*)-*O*-methylmandelic acid (**10**) provided a 7:1 mixture of esters **11a** and **11b**, respectively, in excellent yield (eq 4). Chromatography of the mixture on silica gel provided **11a**, $[\alpha]^{25}_D$ −164 (*c* 1.3, $CHCl_3$), in 83% isolated yield in 98% de. The absolute configuration of each ester was initially deduced[11] by comparing the chemical shifts of the olefinic proton and the methine proton adjacent to the carbon bearing the (*S*)-*O*-methylmandelate present in **11a** and **11b**.



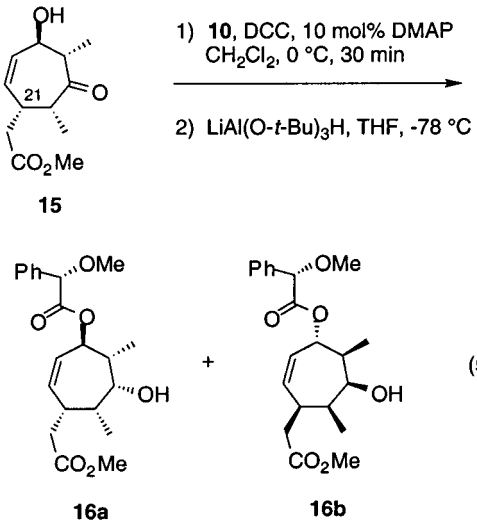
Stereoselective reduction of **11a** with lithium tri-*tert*-butoxyaluminum hydride, followed by methylation of the resulting hydroxyl group under solvent-free conditions,[4a] provided methyl ether **12** in 77% yield (Scheme 1). As the *O*-methylmandelate had served its dual purpose as a resolving agent and a protecting group, it was removed with lithium aluminum hydride. Conversion of **13** into ester-aldehyde **14** was

Scheme 1



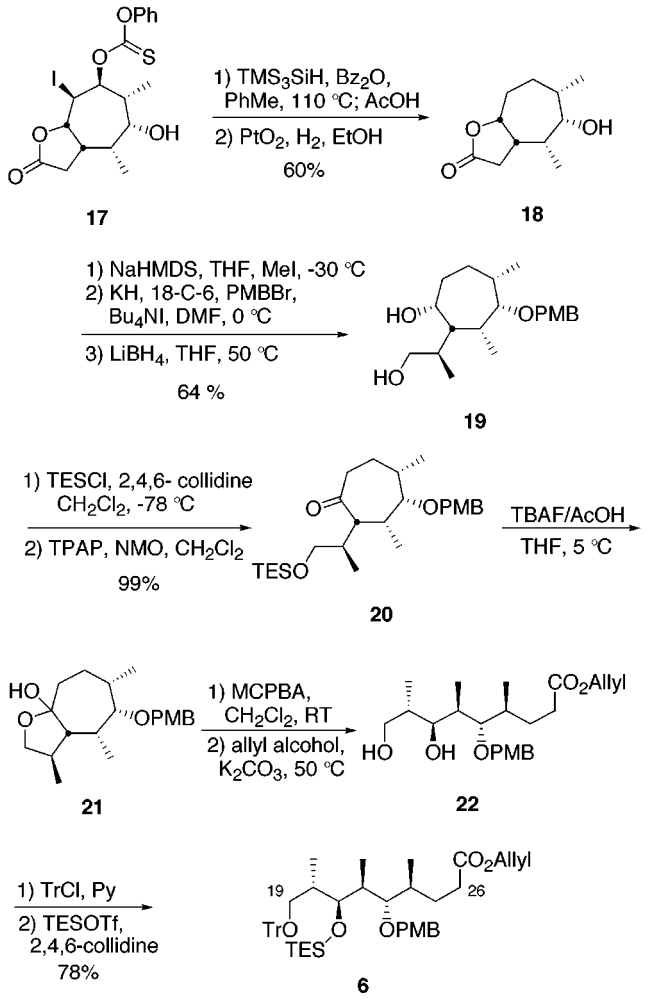
affected by sequential Ley oxidation,[12] dihydroxylation of the crude enone, and exhaustive oxidative cleavage. Chemoselective reduction of the aldehyde, protection of the resulting primary alcohol as a TIPS ether, and reduction of the ester gave rise to the known alcohol **7**, $[\alpha]^{25}_D$ −2.0 (*c* 2.0, $CHCl_3$), lit.[4a] $[\alpha]^{25}_D$ −1.9 (*c* 2.0, $CHCl_3$), in 78% overall yield.

Construction of the C(19)−C(26) fragment of Scytophycin C required treatment of enol silane **2** (75% ee) with 2.0 equiv of 1-methoxy-1-(*tert*-butyldimethylsiloxy)-ethylene in 4.0 M LPDE at 0 °C [eq 1]. Exposure of the crude product to tetra-*n*-butylammonium fluoride (HOAc, THF) provided keto-ester **15** in 83% overall yield. Coupling of **15** with (*S*)-*O*-methylmandelic acid (**10**) provided an inseparable 7:1 mixture of diastereomers in quantitative yield. Stereoselective reduction of the ketone carbonyl with lithium tri-*tert*-butoxyaluminum hydride [eq 5] provided (95%) alcohols **16a** and **16b** in a ratio of 7:1, respectively. Thus, **16a**, $[\alpha]^{25}_D$ −114 (*c* 3.9, $CHCl_3$), could be obtained in 63% isolated yield, 96% de, after chromatography on silica gel.[13]



One-pot saponification and iodolactonization of **16a**, followed by selective formation (PhO(CS)Cl, DMAP) of the thionocarbonate of the least hindered hydroxyl group,

Scheme 2



(6) Interestingly, application of the Simpkins−Koga protocol to bicyclo[3.2.1]octenone **i** employing [*S*-(*R**,*R**)]-(−)-bis(α-methylbenzyl)amine provided the chiral lithium enolate **ii** possessing the assigned absolute configuration [see: Nowakowski, M.; Hoffman, H. M. R. *Tetrahedron Lett.* **1997**, *38*, 1001].

(7) Bunn, B. J.; Cox, P. J.; Simpkins, N. S. *Tetrahedron* **1993**, *49*, 207. Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* **1995**, *36*, 5465.

(8) For the deoxygenation of allylic alcohols employing Et_3SiH/LPDE, see: Wustrow, D. J.; Smith, W. J., III; Wise, L. D. *Tetrahedron Lett.* **1994**, *35*, 61.

(9) A solution of **2** (11.5 g, 43.2 mmol) in 5.0 M LPDE (216 mL, 0.2 M in substrate) was cooled to 0 °C under argon. A solution of DIBALH in toluene (86.4 mL of a 1.0 M solution in toluene, 2.0 equiv) was added over 5 min. The reaction was allowed to warm to ambient temperature and stirred for 20 h. The reaction was cooled to 0 °C and quenched with saturated aqueous potassium sodium tartrate solution, and the product was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo, and purified on silica gel. Elution with 25% ethyl acetate−hexanes provided 5.64 g (65%) of **4**.

provided iodolactone **17** in 70% overall yield. Radical-induced *syn* elimination[14] of **17** (Scheme 2) followed by an acidic workup and reduction of the olefin afforded the saturated lactone **18** in 60% overall yield. Methylation of the dianion-derived lactone **18**, followed by sequential protection of the hydroxyl group as a PMB ether and reduction of the lactone carbonyl, gave way to diol **19**. Silylation of the primary hydroxyl group and subsequent oxidation[12] of the secondary hydroxyl group gave rise to ketone **20**, which upon desilylation provided hemiketal **21**. Direct subjection of **21** to Baeyer−Villiger oxidation[15,16] followed by exposure of the resulting lactones to potassium carbonate in allyl alcohol gave rise to allyl ester **22**. Tritylation of the primary hydroxyl and protection of the secondary hydroxyl as a triethylsilyl ether generated the C(19)−C(26) fragment **6**, $[\alpha]^{25}_{D}$ −4.7 (*c* 1.6, $CHCl_3$).

In summary, desymmetrization of oxabicyclo[3.2.1]-octenone **1** employing [*R*-(*R**,*R**)]-(+)-bis(α-methylbenzyl)-amidolithium **8** provides access to (−)-silyl enol ether **2**, which is capable of undergoing direct bridgehead ring opening with diisobutylaluminum hydride and a silyl ketene acetal affording cycloheptenones **4** and **15**, respectively, which constitute useful substrates for the elaboration of acyclic molecule fragments rich in stereogenic centers.

Acknowledgment. This investigation was supported by a Public Health Service research grant from the National Institute of General Medical Sciences (GM 33605).

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **2**, **4**, **6**, **7**, **11**−**20**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(11) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.

(12) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

(13) Repetitive purification of the remaining (32%) material provided additional **16a** (ca. 20%).

(14) Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040.

(15) Hunt, K. W.; Grieco, P. A. *Org. Lett.* **2000**, *2*, 1717.

(16) Attempts to perform the Baeyer−Villiger oxidation on ketone **20** met with no success.