JOC The Journal of Organic Chemistry

NOTE

pubs.acs.org/joc

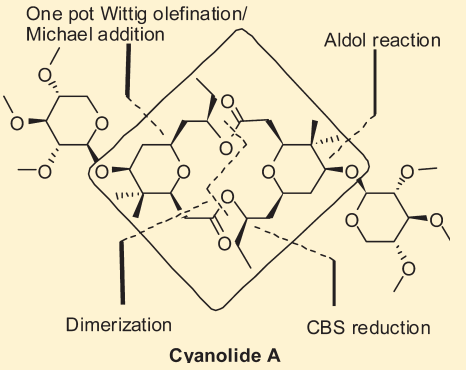
Formal Total Synthesis of Cyanolide A

Srihari Pabbaraja,* K. Satyanarayana, B. Ganganna, and J. S. Yadav

Organic Division-I, Indian Institute of Chemical Technology, CSIR, Hyderabad -500607, India

Supporting Information

ABSTRACT: Formal total synthesis of cyanolide A, aglycosidic dimeric macrolide is accomplished. The key reactions involved are asymmetric acetate aldol reaction, CBS reduction, and Shiina's lactonization.

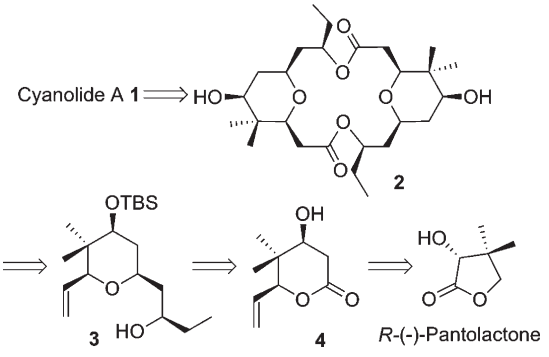


It is estimated that around 207 million people are infected worldwide with schistosomiasis and over 779 million people are at risk of infection.[1] The pathology of schistomiasis includes a complex immune response to schistosome eggs which get trapped in tissues and result in causing hepatomegaly, splenomegaly, bladder cancer, or kidney malfunction and ultimately lead to death.[2] As helminthes require both aquatic snail host and mammalian host to complete their reproductive cycle, simple eradication of the disease in the mammalian host does not protect against the possibility of reinfection if exposed to water containing snail vectors. One fair way would also be to completely eradicate the snail vectors. Cyanolide A, a recently isolated dimeric glycosidic macrolide obtained from extracts of the Papua New Guinea collection of *Lyngbya bouillonii*,[3] was found to be highly toxic against *Biomphalaria glabrata* (LC_{50} = 1.2 μM), which makes it an efficient molluscidal agent. More importantly, this dimeric macrolide was found to be noncytotoxic when tested against H-460 human lung adenocarcinoma and Neuro-2a mouse neuroblastoma cell lines (maximum test concentration of 35 μM).

Owing to the low availability of this natural material for further screening and its utilization, we became interested in taking up the total synthesis of this molecule. The inaugural synthesis[4] has been from Jiyong Hong's group wherein two complementary routes for the total synthesis of cyanolide A have been developed involving tandem allylic oxidation/oxa-Michael reaction and MNBA-mediated dimerization. In the present context, we report a linear and concise approach toward the formal total synthesis of cyanolide A.

Our approach relies on ring expansion of readily available *R*-(−)-pantolactone to six membered lactone **4** achieved through ring-opening, oxidation of free alcohol to aldehyde, asymmetric acetate aldol reaction, and lactonization. Extension of the side chain from the lactone moiety could be achieved by a

Scheme 1. Retrosynthesis



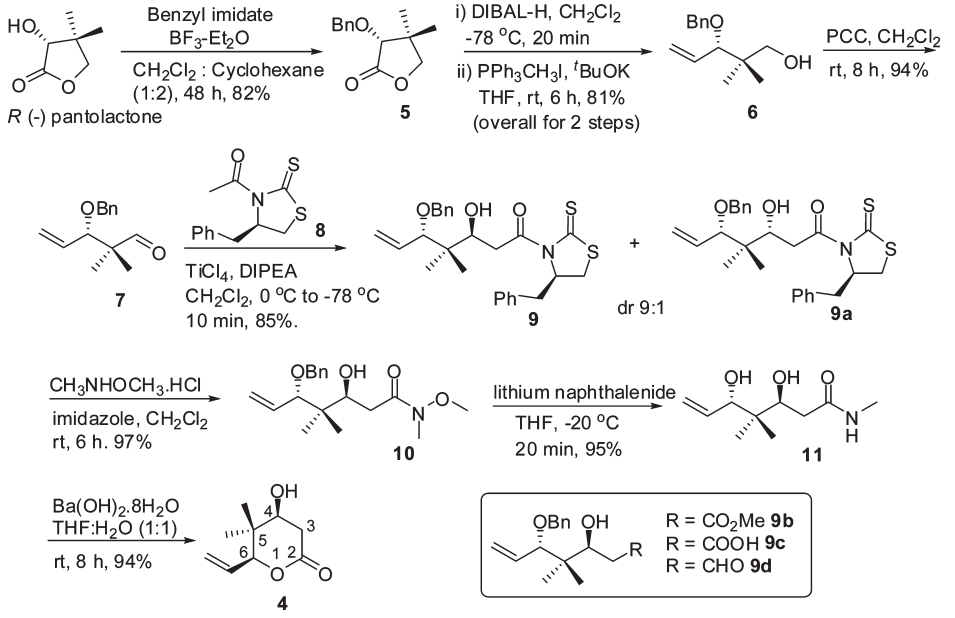
Wittig reaction with 1-(triphenylphosphoranylidene)-2-butanone ylide. Asymmetric reduction of the ketone with CBS catalyst provides the chiral secondary alcohol **3**. Hydroboration and selective oxidation of the vinylic side chain of **3** provides the acid that upon dimerization through Shiina's lactonization (see Scheme 1) can result in the formation of key dimeric macrolide **2**.

The synthesis starts from the readily available chiral raw material *R*-(−)-pantolactone, which was protected as the corresponding benzyl ether by using benzyl imidate catalyzed by $BF_3 \cdot Et_2O$ (Scheme 2).[5] The lactone **5** was reduced to lactal with DIBAL-H and then subjected to one-carbon Wittig homologation reaction to yield alcohol **6**. Oxidation of alcohol **6** with PCC afforded aldehyde **7**, which was subjected to Crimmin's acetate aldol reaction with (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone **8** to yield an inseparable diastereomeric mixture of

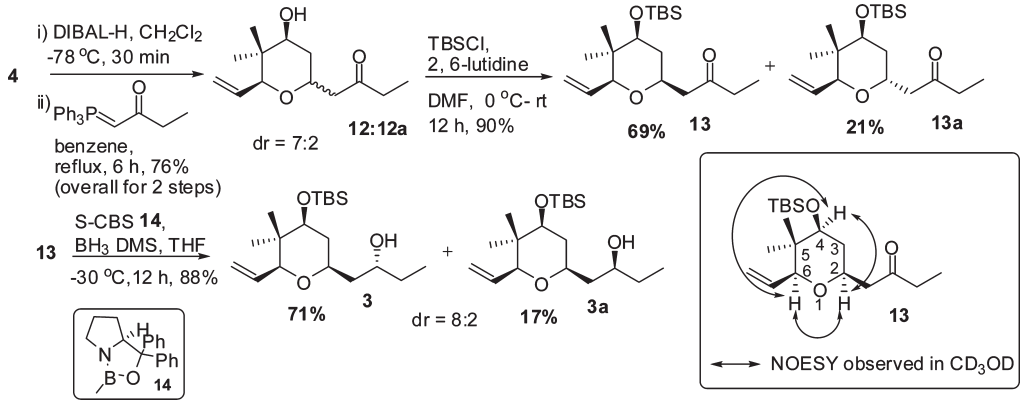
Received: December 4, 2010
Published: January 31, 2011

dx.doi.org/10.1021/jo102401v | *J. Org. Chem.* 2011, 76, 1922–1925

Scheme 2. Synthesis of Lactone 4



Scheme 3. Synthesis of 3



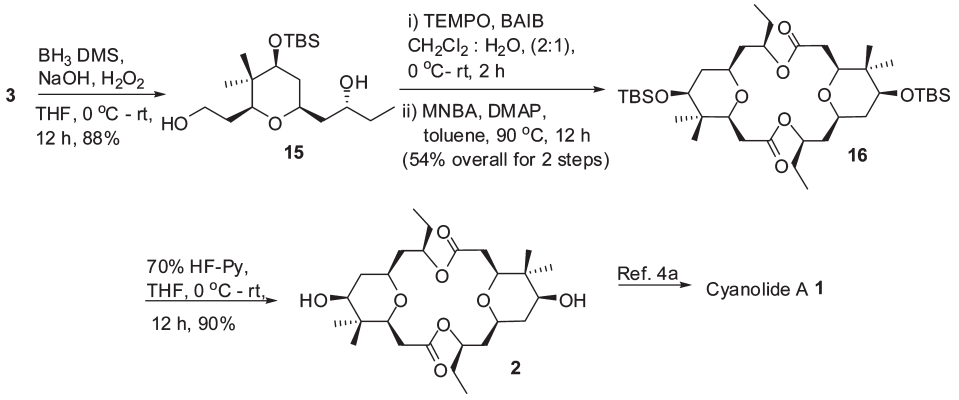
syn and *anti* alcohols **9** and **9a** in 9:1 ratio.[6] With the required geometry set for the secondary alcohol, the next step was to deprotect the benzyl ether and cyclize with auxiliary cleavage through basic hydrolysis. Toward this end, the substrate **9** was converted to ester **9b** with imidazole and MeOH. An attempt to cleave the benzyl ether with lithium naphthalenide at this stage in the presence of ester moiety was not successful and resulted in decomposition of starting material.[7] Hence, compound **9** was directly converted into amide **10** by treating with Weinreb's salt and imidazole. The reaction of amide **10** with lithium naphthalenide proceeded with debenzylation and also cleavage of the *N*−O bond to provide amide **11**. Treatment of **11** with $Ba(OH)_2 \cdot 8H_2O$ provided lactone **4** in good yields.[8]

With the six-membered lactone in hand, the remaining goal was to build up the side chains at both ends on C2 and C6 carbons and proceed toward the total synthesis. Accordingly, the lactone **4** was reduced with DIBAL-H to yield the corresponding lactal, which was treated with 1-(triphenylphosphoranylidene)-2-butanone to yield a mixture of inseparable diastereomers **12** and **12a** in 7:2 ratio following a one-pot Wittig and oxa-Michael reaction (Scheme 3).[9] The compounds **12** and **12a** were protected as their corresponding silyl ethers **13** and **13a** with TBSCl and 2,6-lutidine. The compounds **13** and **13a** were easily separable by column chromatography. The 2D NOESY spectra for compound **13** in CD_3OD[10] revealed the protons geometry to be in *cis* relation at C2, C4, and C6 positions by the presence of strong NOE correlations (see the SI). The keto functionality in **13** was reduced to alcohol by using a catalytic amount of Corey's chiral borane, *S*-CBS catalyst[11] **14** in presence of $BH_3 \cdot DMS$ to yield an easily separable mixture of products **3** and **3a** (dr = 8:2).[12]

The terminal olefin **3** was subjected to hydroboration upon treatment with $BH_3 \cdot DMS$ to yield primary alcohol **15**. Selective oxidation of primary alcohol with TEMPO and BAIB afforded an acid[13] that was directly utilized for dimerization. Thus, the monomeric unit comprised of acid and alcohol functionality was subjected to Shiina's lactonization[14] protocol employing 2-methyl-6-nitrobenzoic anhydride (MNBA) and DMAP to provide dimeric macrolide **16** as previously done by Hong's group.[4] Finally, TBS deprotection with HF-pyridine afforded the

dx.doi.org/10.1021/jo102401v |*J. Org. Chem.* 2011, 76, 1922–1925

Scheme 4. Formal Total Synthesis of Cyanolide A Aglycone



known intermediate cyanolide A aglycone **2**. The spectroscopic data of the synthesized compound, i.e., ^{1}H NMR, ^{13}C NMR, and optical rotation, were compared with those of the earlier known synthesized intermediate[4a] and found to be identical. As this intermediate was already utilized for the total synthesis, we claim a formal total synthesis of cyanolide A (Scheme 4).

In conclusion, a linear approach for the synthesis of cyanolide A aglycone has been described starting from readily available *R*-(−)-pantolactone in 16 steps with an overall yield of 6.6% for the intermediate **2**. The strategy is also being investigated for other analogue synthesis toward the availability of the synthetic material for further biological evaluation. The concise approach with good yields merits its further exploitation toward gram scale synthesis.

EXPERIMENTAL SECTION

(3*S*,5*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-(benzyloxy)-3-hydroxy-4,4-dimethylhept-6-en-1-one (9). To a dry round-bottomed flask under argon atmosphere was added (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone (**8**) (2.3 g, 9.16 mmol) dissolved in CH_2Cl_2 (30 mL). The solution was cooled to 0 °C and titanium tetrachloride (1.2 mL, 10.99 mmol) was added dropwise. The thick suspension was stirred for 10 min upon which diisopropylethylamine (1.89 mL, 10.99 mmol) was added dropwise at 0 °C and stirring was continued. After 10 min the reaction mixture was cooled to −78 °C and to this was added freshly prepared aldehyde **7** (1.6 g, 7.33 mmol) dissolved in CH_2Cl_2 (8 mL). After 10 min the reaction mixture was quenched with aq saturated ammonium chloride solution (10 mL) and warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography with hexane/EtOAc (12:1) to provide a mixture of diasteriomeric (dr = 9:1) product **9** (3.65 g, 85%) as a yellow oil; R_f 0.4 (hexane/EtOAc, 4:1); $[\alpha]^{23}_D$ −141.2 (*c* 0.54, $CHCl_3$); IR (neat) 3468, 2922, 1692, 1260, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.17 (m, 10H), 5.96−5.74 (m, 1H), 5.47−5.22 (m, 3H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 4.23 (d, *J* = 10.6 Hz, 1H), 3.75 (d, *J* = 8.1 Hz, 1H), 3.45−3.16 (m, 5H), 3.10−2.96 (m, 1H), 2.86 (d, *J* = 11.5 Hz, 1H), 0.93 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 173.0, 137.6, 136.4, 134.2, 129.3, 128.7, 128.3, 127.8, 127.6, 127.0, 120.1, 87.7, 73.2, 70.5, 68.7, 41.4, 40.4, 36.5, 32.0, 20.9, 20.6; MS (ESI) *m*/*z* 470 (M + H)$^+$; HRMS (ESI) calcd for $C_{26}H_{32}NO_3S_2$ (M + H)$^+$ 470.1823, found 470.1802.

(*R*)-1-((2*R*,4*S*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-5,5-dimethyl-6-vinyltetrahydro- 2*H*-pyran-2-yl)butan-2-ol (3). To a 25 mL, two-necked, round-bottomed flask charged with a magnetic stir bar was added 0.029 mL of a 1 M solution of (*S*)-CBS **14** in toluene (0.029 mmol). The toluene was then removed by placing the flask on a high-vacuum pump for approximately 1 h. The flask was then placed under argon atmosphere and THF (4 mL) was added. The reaction mixture was cooled to −30 °C and 0.45 mL of a 1 M solution of $BH_3 \cdot S(CH_3)_2$ in THF (0.45 mmol) was added. To this reaction mixture was added dropwise a solution of ketone **13** (100 mg, 0.294 mmol) dissolved in THF (1 mL). The reaction was stirred for 12 h at −30 °C before MeOH (∼3 mL) was carefully added to destroy excess BH_3. The reaction was diluted with saturated aqueous NH_4Cl (∼2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude oil was purified by flash chromatography with hexane/EtOAc (22:1), giving dr = 8:2 (70.8 mg with 71% major isomer **3**, 17.7 mg with 17% minor isomer **3a** as a colorless oil). R_f 0.4 (hexane/EtOAc, 9:1). **Major isomer 3:** $[\alpha]^{23}_D$ +7.30 (*c* 0.92, $CHCl_3$); IR (neat) 3445, 2925, 2853, 1252, 1095, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88−5.70 (m, 1H), 5.20 (s, 1H), 5.16 (d, *J* = 4.5 Hz, 1H), 3.77−3.57(m, 3H), 3.50 (d, *J* = 6.4 Hz, 1H), 3.44−3.35 (m, 1H), 1.71−1.31 (m, 6H), 0.98−0.87 (m, 12H), 0.84 (s, 3H), 0.81 (s, 3H), 0.05 (d, *J* = 2.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 117.3, 85.1, 75.6, 73.5, 41.8, 39.2, 38.1, 30.3, 25.8, 23.1, 18.0, 14.1, 12.7, 9.8, −3.9, −4.9; MS (ESI) *m*/*z* 343 (M + H)$^+$; HRMS (ESI) calcd for $C_{19}H_{38}O_3NaSi$ (M + Na)$^+$ 365.2487, found 365.2479. **Minor isomer 3a:** $[\alpha]^{23}_D$ +78.30 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84−5.72 (m, 1H), 5.24−5.10 (m, 2H), 3.85−3.76 (m, 1H), 3.74−3.65 (m, 1H), 3.46−3.39 (m, 2H), 1.70−1.57 (m, 3H), 1.52−1.39 (m, 3H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.90 (s, 9H), 0.85 (s, 3H), 0.80 (s, 3H), 0.05 (d, *J* = 2.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 117.1, 85.2, 76.3, 73.6, 69.8, 41.8, 39.4, 37.5, 30.5, 26.1, 23.3, 18.2, 13.2, 10.3, −3.6, −4.6.

Diolide 16. To a vigorously stirred solution of alcohol **15** (40 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) and H_2O (1 mL) was added TEMPO (6.9 mg, 0.04 mmol) and BAIB (178 mg, 0.55 mmol). Stirring was continued until TLC indicated complete conversion of the starting material. The reaction mixture was quenched by the addition of saturated $Na_2S_2O_3$ solution (5 mL). The mixture was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was employed in the next step without further purification. To a solution of 2-methyl-6-nitrobenzoic anhydride (MNBA, 114.5 mg, 0.33 mmol) and DMAP (270 mg, 2.22 mmol) in toluene (50 mL) was slowly added the above acid in toluene (15 mL) by a syringe pump at 90 °C for 12 h. The reaction mixture was concentrated under vacuum. The residue was purified by column chromatography with hexane/EtOAc (10:1) to afford **16** as a colorless oil (21.3 mg, 54%). R_f 0.7 (hexane/EtOAc, 9:1); $[\alpha]^{25}_D$ −1.5 (*c* 0.79, $CHCl_3$); IR (neat)

dx.doi.org/10.1021/jo102401v |*J. Org. Chem.* 2011, 76, 1922–1925

1718, 1463, 1206, 1092, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (dd, J = 7.6, 6.8 Hz, 2H), 3.47−3.35 (m, 6H), 2.45−2.20 (m, 4H), 1.91−1.76 (m, 2H), 1.72−1.48 (m, 8H), 1.34 (q, J = 12.8, 11.3 Hz, 2H), 0.89 (s, 18H), 0.87−0.78 (m, 18H), 0.06 (d, J = 3.8 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 80.4, 75.7, 74.9, 73.6, 40.9, 39.0, 37.9, 35.4, 28.2, 25.8, 22.8, 18.0, 12.8, 9.5, −3.9, −4.9; MS (ESI) m/z 713 $(M + H)^+$; HRMS (ESI) calcd for $C_{38}H_{72}O_8NaSi_2$ $(M + Na)^+$ 735.4663, found 735.4644.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and ^1H NMR and ^{13}C NMR spectra of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
srihari@iict.res.in

■ ACKNOWLEDGMENT

K.S. thanks UGC, New Delhi and B.G. thanks CSIR, New Delhi for the award of fellowships toward financial assistance. P.S. acknowledges research grant (P 81-113) from Human Resources Research Group-New Delhi through the Council of Scientific & Industrial Research (CSIR) Young Scientist Award Scheme.

■ REFERENCES

(1) (a) Steinmann, P.; Keiser, J.; Bos, R.; Tanner, M.; Utzinger, J. *Lancet Infect. Dis.* **2006**, *6*, 411–425. (b) Chitsulo, L.; Engels, D.; Montresor, A.; Savioli, L. *Acta Trop.* **2000**, *77*, 41–51.

(2) (a) World Health Organization. *Report of the Scientific Working Group Meeting on Schistosomiasis*, Geneva, Switzerland, Nov 14−16, 2005.(b) Gryseels, B.; Polman, K.; Clerinx, J.; Kestens, L. *Lancet* **2006**, *368*, 1106–1118.

(3) Pereira, A. R.; McCue, C. F.; Gerwick, W. H. *J. Nat. Prod.* **2010**, *73*, 217–220.

(4) (a) Kim, H.; Hong, J. *Org. Lett.* **2010**, *12*, 2880–2883. While preparing our manuscript and being considered for publication, two other contributions have appeared on the web; see: (b) Yang, Z.; Xie, X.; Jing, P.; Zhao, G.; Zheng, J.; Zhao, C.; She X. *Org. Biomol. Chem.* **2011** DOI: 10.1039/C0OB00971G. Published Online: Dec 13, 2010. (c) Hajare, A. K.; Ravikumar, V.; Khaleel, S.; Bhuniya, D.; Reddy, D. S. *J. Org. Chem.* **2011**, DOI: 10.1021/jo101782q. Published Online Dec 31, 2010.

(5) (a) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240–1241. (b) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738–3740.

(6) Procedures for aldol reaction were adapted from: (a) Srihari, P.; Rajendar, G.; Srinivasa Rao, R.; Yadav, J. S. *Tetrahedron Lett.* **2008**, *49*, 5590–5592. (b) Yadav, J. S.; Kumar, V. N.; Rao, R. S.; Srihari, P. *Synthesis* **2008**, 1938–1942. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894–902. (d) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029–2032. (e) Hodge, M. B.; Olivo, H. F. *Tetrahedron* **2004**, *60*, 9397–9403. The ratio was determined based on ^1H NMR.

(7) Attempts for debenzylation on the substrate with acid **9c** and aldehyde **9d** functional groups employing lithium naphthalenide resulted in decomposition of the starting material.

(8) A similar procedure was followed as reported in: Lukes, R.; Cerny, M. *Collect. Czech. Chem. Commun.* **1952**, *23*, 946–953.

(9) The ratio was determined based on the ^1H NMR spectrum.

(10) As the protons were merged in $CDCl_3$, the NOESY spectrum was not supportive for all *syn* geometry (for C2, C4, and C6 protons). However, In CD_3OD, the NOESY was clear to support the *syn* geometry for all three protons.

(11) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. (b) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611–614. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

(12) The ratio was based on the yield of the isolated products after column chromatography.

(13) A similar procedure was adapted as given in: Yadav, J. S.; Suresh Reddy, Ch. *Org. Lett.* **2009**, *8*, 1705–1708.

(14) (a) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822–1830. (b) Shiina, I.; Fukui, S.; Sasaki, A. *Nat. Protoc.* **2007**, *2*, 2312–2317.

■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on Jan 31, 2011, with errors in Scheme 1 and the Supporting Information. The corrected version was reposted on Feb 23, 2011.