Angewandte Chemie International Edition

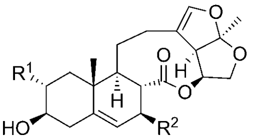
DOI: 10.1002/anie.201101893

Natural Product Synthesis

Biomimetic Synthesis of 5,6-dihydro-glaucogenin C: Construction of the Disecopregnane Skeleton by Iron(II)-Promoted Fragmentation of an α-Alkoxy Hydroperoxide

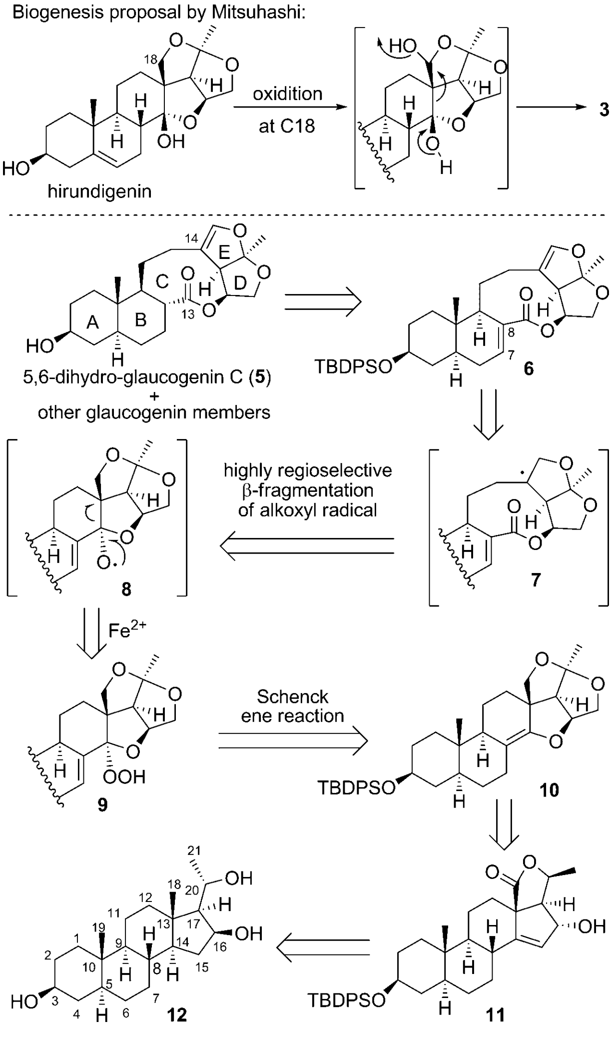
*Jinghan Gui, Dahai Wang, and Weisheng Tian**

Natural products that have rearranged steroid skeletons and promising biological activity have attracted significant attention in the field of synthetic chemistry in recent years, with the most representative examples being cortistatins[1] and nakiterpiosin.[2] Another representative example of such natural products is the glaucogenin family (**1–4**), which is a collection of unique 13,14:14,15-disecopregnane steroids. In the 1980s, Mitsuhashi and co-workers isolated these unusual C21 steroids from the hydrolysates of crude glycosides in three Chinese herbal medicines "Bai-Qian (*Cynanchum glaucescens*)", "Bai-Wei (*Cynanchum atratum*)", and "Xu-Chang-Qing (*Cynanchum paniculatum*)", which all belong to the Asclepiadaceae plant family.[3] The structure and configuration of this class of compounds were established unequivocally by X-ray crystallographic analysis of the diacetate of glaucogenin C mono-D-thevetoside.[3a,b] Recent biological studies on glaucogenin C and its four glycosides revealed that they were effective and selective inhibitors of alphavirus-like positive-strand RNA viruses but not of other RNA or DNA viruses, yet they showed no toxicity to host cells.[4] The IC$_{50}$ values of glaucogenin C (17 nM) and its four glycosidal derivatives (each 25 nM) suggest that it is the aglycon unit and not the linked oligosaccharide chains that is in fact responsible for the inhibitory effect. Despite the unique chemical structure and powerful antiviral activity of the glaucogenin family, no chemical synthesis of these steroids has been reported to date. Herein, we report the first synthesis of 5,6-dihydro-glaucogenin C (**5**) from (16S,20S)-5α-pregnane-3β,16,20-triol (**12**), which is a readily available C21 steroid obtained from tigogenin[5] that provides a general and biomimetic approach to 13,14:14,15-disecopregnane steroids.[6]



R^1 = OH, R^2= H, glaucogenin A (**1**)
R^1 = OH, R^2= OH, glaucogenin B (**2**)
R^1 = H, R^2= H, glaucogenin C (**3**)
R^1 = H, R^2= OH, glaucogenin D (**4**)

The synthetic challenge posed by the glaucogenin family lies, in great part, in the stereoselective construction of the highly functionalized D/E rings and scission of the C13–C14 single bond to form the nine-membered lactone ring. As shown in Scheme 1, we envisaged that the target molecule **5** and other glaucogenin members could be accessed from unsaturated ester **6** through reduction and transposition of the



Scheme 1. Retrosynthetic analysis of 5,6-dihydro-glaucogenin C and other members of the glaucogenin family. TBDPS = *tert*-butyldiphenylsilyl.

---

[*] J. Gui, Dr. D. Wang, Prof. Dr. W. Tian
Key Laboratory of Synthetic Chemistry of Natural Substances
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (China)
Fax: (+86) 21-5492-5176
E-mail: wstian@mail.sioc.ac.cn

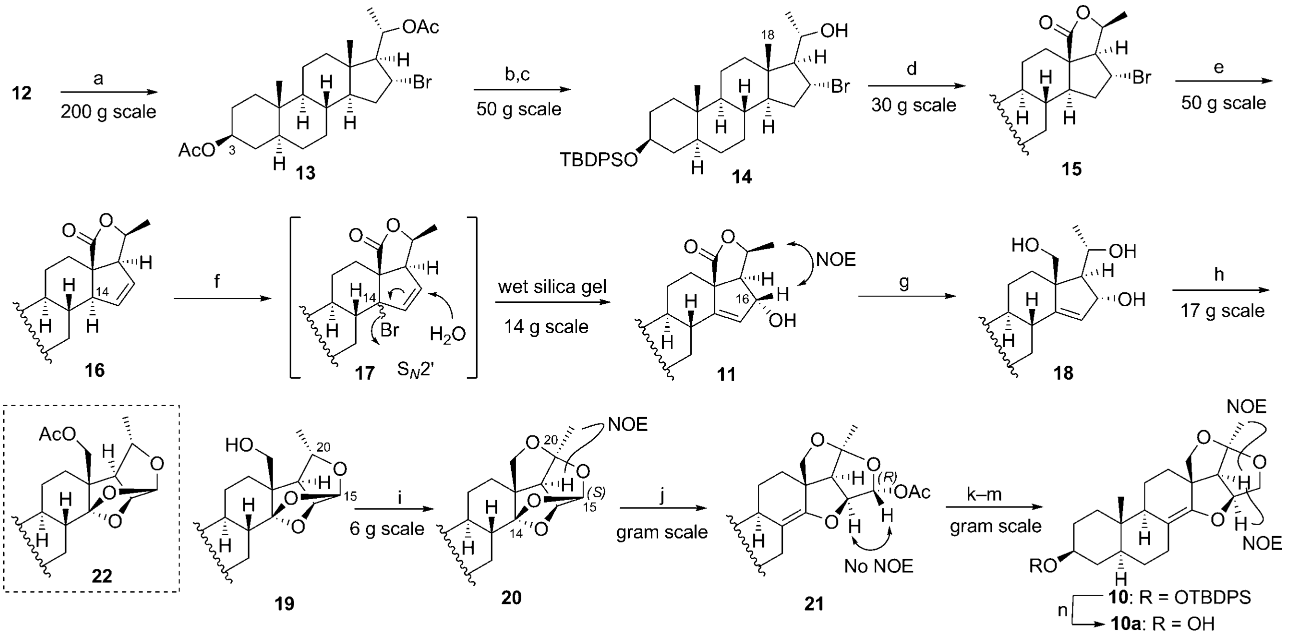
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201101893.

C7–C8 olefin, respectively. A biogenetic pathway proposed by Mitsuhashi et al. suggested that the key nine-membered lactone ring might be generated from hirundigenin through hydroxylation at C18 and subsequent Grob-type fragmentation (Scheme 1, top equation).[3a,b] Inspired by this biogenesis, we surmised that such bond scission could also be accomplished through β-fragmentation of the alkoxy radical **8** without preoxidation at C18. In this regard, the iron/copper-promoted fragmentation reaction of alkoxy hydroperoxide[7] appeared to be an attractive approach. The alkoxy hydroperoxide **9** in turn might be prepared from the key intermediate **10** by the Schenck ene reaction.[8] Intermediate **10** could then be traced back to **12** through stereoselective synthesis of allylic alcohol **11**.

The first objective of our synthesis was to develop a scalable route to **10** on the way to **5** and other glaucogenin members. As depicted in Scheme 2, the synthesis commenced with bromination/acetylation of **12** (69%, 200 g scale),[9] and subsequent ester hydrolysis and selective protection of the hydroxy group at C3 (quant., 50 g scale) to give **14** in large quantities. Proximal functionalization of the unactivated angular methyl group at C18 in **14** by using the method developed by Meystre and co-workers[10a] provided the desired lactone **15** (84%, 30 g scale),[10b–d] whose elimination using DBU in toluene at reflux then led to the desired alkene **16** (quant., 50 g scale) with absolute regiocontrol.

It was postulated that the transformation involving the stereoselective installation of the hydroxy group at C16 with a concomitant double bond shift could be effected by introducing a leaving group at C14, followed by an S_N2' reaction involving H_2O.[11] On the basis of this consideration and previous work carried out within our research group,[12] we were pleased to find that exposure of **16** to radical bromination condition (NBS, AIBN) afforded a major product, which was converted into the allylic alcohol **11** with the required α configuration at C16 during chromatography on silica gel (53% yield). The stereoselectivity of this reaction is believed to originate from attack at the *Si* face of water on the initially formed allylic bromination product **17**.[13] Unfortunately, when this reaction was performed on a larger scale, the yield was variable (24–48%). Efforts to optimize this reaction eventually revealed that the use of 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (DBDMH)[14] as the brominating reagent and subsequent treatment with wet silica gel could deliver **11** in reproducible 72% yield on a 14 g scale.

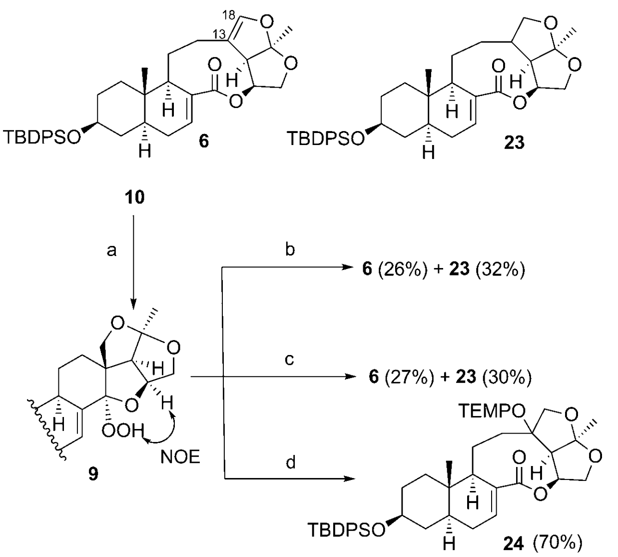
With the hydroxy group at the C16 stereogenic center now introduced, the preparation of **10** was then investigated. The two-step procedure of reduction of lactone **11** using $LiAlH_4$ in conjunction with subsequent oxidative olefin cleavage resulted in the formation of **19** (93%, 17 g scale), the structure of which was confirmed by NMR characterization of its acetylation product **22**. To access **10**, an efficient and chemoselective oxidation of the ether at C20 and reduction of the acetal at C15 were required. To this end, **19** was subjected to a second remote intramolecular free radical functionalization[15] to afford the cage-like C20-oxidized product **20** (82%, 6 g scale) with an interesting consecutive ketal/acetal/ketal linkage. The next task, that is, selective reduction of the acetal



Scheme 2. Gram-scale synthesis of key intermediate **10**. Reagent and conditions: a) 33% HBr/HOAc, 40°C, 2 h, 69%; b) $LiOH·H_2O$, THF/MeOH (1:4), 80°C, 1 h; c) TBDPSCl, imidazole, CH_2Cl_2, RT, 1 h, quant. (2 steps); d) $Pd(OAc)_4$, I_2, $CaCO_3$, cyclohexane, *hν*, 2 h, then Jones oxidation, 84%; e) DBU, toluene, reflux, 1 day, 97%; f) DBDMH, AIBN, CCl_4, cyclohexene oxide, reflux, 1 h, then wet silica gel, CH_2Cl_2, RT, 10 h, 72%; g) LAH, THF, 50°C, 1 h; h) O_3, CH_2Cl_2, −78°C, 40 min, then Zn-HOAc, RT, 1 day, 93% (2 steps); i) DIB, I_2, cyclohexane, *hν*, 1 h, 82%; j) PPTS, Ac_2O, 130°C, 2 h, 72%; k) Et_3N, MeOH, 50°C, 9 h; l) MsCl, Et_3N, CH_2Cl_2, 0°C, 3 h; m) LAH, THF, RT, 1 h, 70% (3 steps); n) TBAF, THF, 60°C, quant. AIBN = azobisisobutyronitrile, DBDMH = 1,3-dibromo-5,5-dimethylhydantoin, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIB = (diacetoxyiodo)benzene, LAH = lithium aluminum hydride, Ms = methanesulfonyl, PPTS = pyridinium 4-toluenesulfonate, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

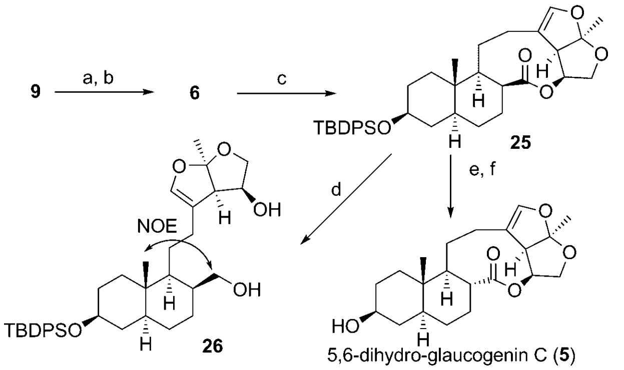
at C15 in the presence of ketals at C20 and C14 proved to be exceedingly challenging, as various direct reduction conditions resulted in either no reaction or overreduction of the ketal at C14. Ultimately, however, this problem was solved by first converting **20** into the enol ether **21** (72 %, gram scale) having an inverted configuration at C15,[16] and then reducing the acetal at C15 by a one-pot, three-step procedure involving ester hydrolysis, mesylation, and reduction using $LiAlH_4$ to furnish **10** in 70 % overall yield (gram scale). Removal of the TBDPS protecting group of **10** (TBAF, THF) then afforded a known compound, dihydro-anhydrohirundigenin (**10a**), whose ^1H NMR spectrum was in good agreement with that reported.[17]

As anticipated, the Schenck ene reaction[8] of **10** afforded the alkoxy hydroperoxide **9** in quantitative yield and in a highly regio- and stereoselective manner, and thus set the stage for the key fragmentation reaction (Scheme 3). Treatment of **9** with known condition ($FeSO_4$, $Cu(OAc)_2$)[7a–d] gave the desired disecopregane product **6** in only 26 % yield, together with 32 % of the 13,18-dihydro derivative **23**. According to Schreiber's proposed mechanism,[7d] the olefin at C13–C18 is formed via β-hydrogen elimination of the alkyl copper intermediate generated by the oxidative coupling of carbon radical **7** with $Cu(OAc)_2$ (Scheme 1). To elucidate the role of $Cu(OAc)_2$ in the reaction, a control experiment was conducted in the absence of $Cu(OAc)_2$, and surprisingly, **6** and **23** were also isolated in 27 % and 30 % yield, respectively. The nearly 1:1 ratio of **6** and **23** suggested that they might be produced through disproportionation of **7**. On the basis of the above results, we hypothesized that the ferrous-mediated homolytic cleavage of the peroxide and subsequent alkoxy radical fragmentation were highly efficient. Meanwhile, $Cu(OAc)_2$ showed little reactivity toward olefin production in our system. To test this hypothesis, the initially formed tertiary carbon radical **7** was trapped with TEMPO, which indeed afforded the desired product **24** in 70 % yield.



Scheme 3. Construction of the key nine-membered lactone by iron(II)-promoted regioselective fragmentation reaction of α-alkoxy hydroperoxide. Reagent and conditions: a) TPP, O_2, CH_2Cl_2, *hν*, 0 °C, 1 h, quant.; b) $FeSO_4$, $Cu(OAc)_2$, MeOH, RT, 1 h; c) $FeSO_4$, MeOH, RT, 1 h; d) $FeSO_4$, TEMPO, MeOH, RT, 1 h. TEMPO = 2,2,6,6-tetramethylpiperidin-1-yloxyl, TPP = 5,10,15,20-tetraphenyl-21H,23H-porphine.

To continue the synthesis, TEMPO was substituted with I_2 for ease of elimination during installation of the olefin at C13–C18. In the event, treatment of **9** with $FeSO_4$ and I_2 followed immediately by highly regioselective HI elimination afforded **6** in a striking 69 % yield over two steps (Scheme 4).



Scheme 4. Completion of the synthesis of 5,6-dihydro-glaucogenin C. Reagent and conditions: a) $FeSO_4$, I_2, MeOH, RT, 1 h; b) DBU, toluene, 80 °C, 1 h, 69 % (2 steps); c) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, THF/MeOH (2:3), 0 °C to RT, 73 %; d) LAH, THF, 45 °C, 1.5 h, 66 %; e) TBAF, THF, 60 °C, 13 h, 92 %; f) NaH, THF, 80 °C, 2 h, 90 %.

Then, hydrogenation of the electron-deficient alkene in **6** (73 %),[18] and subsequent removal of the protecting group (92 %) and epimerization (90 %) completed the synthesis of **5**, whose ^{13}C NMR data of the D/E rings was in accordance with the data reported for glaucogenin C.[3f] The configuration of the hydrogenated product **25** was deduced from the NOE interactions of its reduced derivative **26**.

In conclusion, we have achieved the first biomimetic synthesis of 5,6-dihydro-glaucogenin C in 19 steps from (16*S*,20*S*)-5α-pregnane-3β,16,20-triol (**12**) in an overall yield of 6.4 %. The key features of our synthesis were: 1) radical bromination (S_N2' reaction) to set the stereogenic center at C16, 2) oxidation of Me and ether groups at C18 and C21, respectively, by two remote intramolecular free radical functionalizations, 3) high scalability of the synthetic route to key intermediate **10**; and most importantly, 4) Schenck ene reaction and subsequent iron(II)-promoted regioselective fragmentation reaction of α-alkoxy hydroperoxide to construct the key nine-membered lactone ring of **6**. Our modified Schreiber procedure, that is, replacing $Cu(OAc)_2$ with a free radical trapping reagent (I_2 or TEMPO), may be applicable to the synthesis of other macrolides. Furthermore, the presence of the olefin at C7–C8 in our synthesis may provide us the opportunity to introduce the olefin at C5–C6 for the synthesis of the natural product, glaucogenin C, as well as other members of the glaucogenin family. This endeavor is the subject of our current research and will be reported in due course.

Received: March 17, 2011
Published online: June 17, 2011

Keywords: alkoxy hydroperoxide · biomimetic synthesis · fragmentation · iron · natural products

---

[1] For reviews, see: a) D. Y.-K. Chen, C.-C. Tseng, *Org. Biomol. Chem.* **2010**, *8*, 2900; b) A. R. Hardin Narayan, E. M. Simmons, R. Sarpong, *Eur. J. Org. Chem.* **2010**, 3553; c) Y. Shi, W. Tian, *Chin. J. Org. Chem.* **2010**, *30*, 515, and references therein.

[2] a) T. Ito, M. Ito, H. Arimoto, H. Takamura, D. Uemura, *Tetrahedron Lett.* **2007**, *48*, 5465; b) S. Gao, Q. Wang, C. Chen, *J. Am. Chem. Soc.* **2009**, *131*, 1410; c) H. Takamura, Y. Yamagami, T. Ito, M. Ito, H. Arimoto, I. Kadota, D. Uemura, *Heterocycles* **2009**, *77*, 351; d) S. Gao, Q. Wang, L. J.-S. Huang, L. Lum, C. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 371.

[3] a) T. Nakagawa, K. Hayashi, H. Mitsuhashi, *Tetrahedron Lett.* **1982**, *23*, 757; b) T. Nakagawa, K. Hayashi, H. Mitsuhashi, *Chem. Pharm. Bull.* **1983**, *31*, 870; c) T. Nakagawa, K. Hayashi, H. Mitsuhashi, *Chem. Pharm. Bull.* **1983**, *31*, 2244; d) T. Nakagawa, K. Hayashi, H. Mitsuhashi, *Chem. Pharm. Bull.* **1983**, *31*, 879; e) T. Nakagawa, K. Hayashi, K. Wada, H. Mitsuhashi, *Tetrahedron* **1983**, *39*, 606; f) Z. Zhang, J. Zhou, K. Hayashi, H. Mitsuhashi, *Chem. Pharm. Bull.* **1985**, *33*, 1507; g) Z. X. Zhang, J. Zhou, K. Hayashi, H. Mitsuhashi, *Chem. Pharm. Bull.* **1985**, *33*, 4188; h) K. Sugama, K. Hayashi, H. Mitsuhashi, K. Kaneko, *Chem. Pharm. Bull.* **1986**, *34*, 4500; i) J. Dou, Z.-M. Bi, Y.-Q. Zhang, P. Li, *Chin. J. Nat. Med.* **2006**, *4*, 192.

[4] Y. Li, L. Wang, S. Li, X. Chen, Y. Shen, Z. Zhang, H. He, W. Xu, Y. Shu, G. Liang, R. Fang, X. Hao, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 8083.

[5] a) W. Tian, CN 1146457A, **1997**; b) W. Tian, M. Li, H. Yin, X. Tang, CN 1299821A, **2001**; c) W. Tian, S. Liu, J. Shen, CN 1341603A, **2002**; d) W. Tian, S. Liu, B. Qiu, X. Wu, CN 1475494A, **2004**.

[6] For a biomimetic approach to C-nor-D-homo-steroids (such as nakiterpiosin), see: P. Heretsch, S. Rabe, A. Giannis, *J. Am. Chem. Soc.* **2010**, *132*, 9968.

[7] a) S. L. Schreiber, T. Sammakia, B. Hulin, G. Schulte, *J. Am. Chem. Soc.* **1986**, *108*, 2106; b) S. L. Schreiber, B. Hulin, W. F. Liew, *Tetrahedron* **1986**, *42*, 2945; c) S. L. Schreiber, W. Liew, *J. Am. Chem. Soc.* **1985**, *107*, 2980; d) S. L. Schreiber, *J. Am. Chem. Soc.* **1980**, *102*, 6163; for early reports on alkyl hydroperoxides, see: e) Z. Cekovió, L. Dimitrijevic, G. Djokic, T. Srnic, *Tetrahedron* **1979**, *35*, 2021; f) Z. Cekovió, M. M. Green, *J. Am. Chem. Soc.* **1974**, *96*, 3000.

[8] a) H. H. Wasserman, R. W. Murray, *Singlet Oxygen*, Academic Press, New York, **1979**; b) A. A. Frimer, *Chem. Rev.* **1979**, *79*, 359; c) M. Prein, W. Adam, *Angew. Chem.* **1996**, *108*, 519; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 477; d) E. L. Clennan, *Tetrahedron* **2000**, *56*, 9151; e) M. Stratakis, M. Orfanopoulos, *Tetrahedron* **2000**, *56*, 1595.

[9] J. Lin, J. Wang, L. Chen, Y. Wang, X. Tang, Q. Xu, Z. Zhu, W. Tian, *Acta Chim. Sin.* **2006**, *64*, 1265.

[10] a) K. Heusler, P. Wieland, C. Meystre, *Org. Synth.* **1965**, *45*, 57; b) S. Bhandaru, P. L. Fuchs, *Tetrahedron Lett.* **1995**, *36*, 8347; c) Y. Shi, L. Jia, Q. Xiao, Q. Lan, X. Tang, D. Wang, M. Li, Y. Ji, T. Zhou, W. Tian, *Chem. Asian J.* **2011**, *6*, 786; d) G. Majetich, K. Wheless, *Tetrahedron* **1995**, *51*, 7095.

[11] For such S_N2' reactions with H_2O as the leaving group, see: a) W. Li, P. L. Fuchs, *Org. Lett.* **2003**, *5*, 2849; b) J. S. Lee, P. L. Fuchs, *J. Am. Chem. Soc.* **2005**, *127*, 13122.

[12] L. Jia, PhD thesis, Shanghai Institute of Organic Chemistry (China), **2002**.

[13] When this S_N2' reaction proceeded intramolecularly, the opposite stereoselectivity would result, see Ref. [11b].

[14] L. Vanmaele, P. J. De Clercq, M. Vandewalle, *Tetrahedron* **1985**, *41*, 141.

[15] P. de Armas, J. I. Concepcion, C. G. Francisco, R. Hernandez, J. A. Salazar, E. Suarez, *J. Chem. Soc. Perkin Trans. 1* **1989**, 405.

[16] Modified conditions to those reported in the literature: K. Ravindar, M. S. Reddy, L. Lindqvist, J. Pelletier, P. Deslongchamps, *Org. Lett.* **2010**, *12*, 4420.

[17] a) K. Stoeckel, W. Stoecklin, T. Reichstein, *Helv. Chim. Acta* **1969**, *52*, 1403; b) K. Stoeckel, W. Stoecklin, T. Reichstein, *Helv. Chim. Acta* **1969**, *52*, 1429; c) R. Imhof, F. Marti, B. P. Schaffner, H. Wehrli, *Helv. Chim. Acta* **1973**, *56*, 1920.

[18] M. Seki, T. Shimizu, K. Matsumoto, *J. Org. Chem.* **2000**, *65*, 1298.