ORGANIC LETTERS

2004
Vol. 6, No. 25
4723−4726

Validation of Lanthanide Chiral Shift Reagents for Determination of Absolute Configuration: Total Synthesis of Glisoprenin A

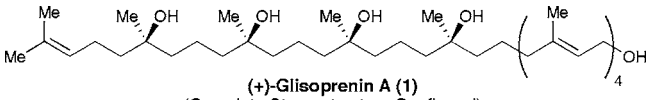
Christopher M. Adams, Indranath Ghosh, and Yoshito Kishi*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

kishi@chemistry.harvard.edu

Received September 23, 2004

ABSTRACT



(+)-Glisoprenin A (1)
(Complete Stereostructure Confirmed)

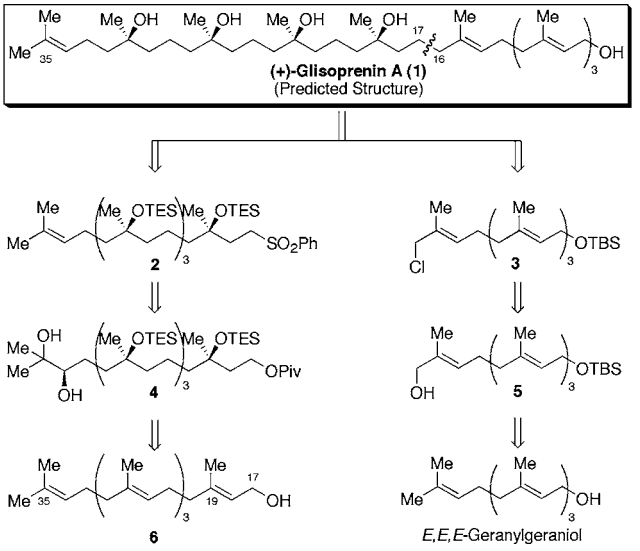
The complete stereostructure of the natural product (+)-glisoprenin A had been predicted via a novel application of chiral lanthanide shift reagents. Confirmation of the predicted stereostructure of (+)-glisoprenin A and validation of the chiral lanthanide shift approach have now been achieved through total synthesis.

In the preceding Letters,[1,2] we have introduced a novel approach for the determination of absolute configuration of secondary and tertiary alcohols and used this method to predict the complete stereostructure of the natural product (+)-glisoprenin A. In this Letter, we address the validity of this approach by confirming our stereochemical assignment via total synthesis.

(+)-Glisoprenin A (**1**) is a novel acyl Co-A transferase inhibitor isolated by Omura and co-worker in 1992 from the fermentation broth of *Gliocladium* sp. FO-1513.[3] Extensive one- and two-dimensional NMR experiments combined with mass spectra analysis led Omura to propose a polyprenoid skeleton bearing four tertiary hydroxyls as the constitutional structure for (+)-**1**. Further work in our laboratories, as elaborated in the preceding Letter,[2] has led us to predict the complete stereostructure depicted in Scheme 1. To confirm both the predicted constitutional and stereochemical (relative and absolute) structure of (+)-**1**, we embarked on the total synthesis of (+)-glisoprenin A.

Retrosynthetically, we envisioned disconnection of the C-16/C-17 bond to furnish sulfone **2** and allyl chloride **3**, available from (*E*,*E*,*E*)-geranylgeraniol (Scheme 1). Sulfone

Scheme 1



(1) Ghosh, I.; Zeng, H.; Kishi, Y. *Org. Lett.* **2004**, *6*, 4715.
(2) Ghosh, I.; Kishi, Y.; Tomoda, H.; Omura, S. *Org. Lett.* **2004**, *6*, 4719.
(3) (a) Tomoda, H.; Huang, X.-H.; Nishida, H.; Masuma, R.; Kim, Y. K.; Omura, S. *J. Antibiot.* **1992**, *45*, 1202. (b) Nishida, H.; Huang, X.-H.; Tomoda, H.; Omura, S. *J. Antibiot.* **1992**, *45*, 1669.

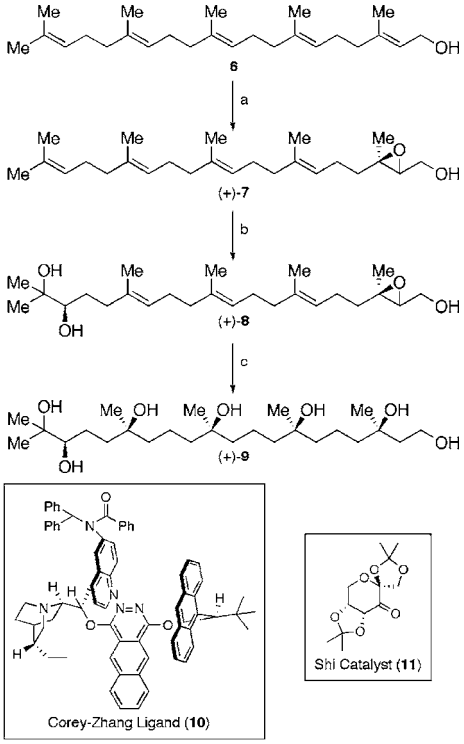
10.1021/ol048059o CCC: $27.50
Published on Web 11/06/2004

2 would derive from the diol **4**. A series of chemoselective and stereoselective oxidations would then reveal the known polyprenol **6**.[4] Specifically, we envisioned that the Shi epoxidation protocol,[5] followed by reductive oxirane opening, could be used to install the requisite tertiary hydroxyls. Clearly, this strategy would require the temporary protection of the terminal isopropylidene unit, which could be accomplished via chemoselective dihydroxylation.[6]

To this end, the known polyprenol **6**[4] was synthesized in six steps from geraniol according to the protocol developed by Radetich and Corey.[4] The stage was then set for dihydroxylation of the terminal isopropylidene unit[6] and Shi epoxidation.[5] However, model studies used to determine the optimal conditions for the Shi epoxidation, coupled with results by McDonald and co-workers,[7] indicated that epoxidation of the C-18/C-19 olefin may prove to be problematic due to the electron-withdrawing nature of the pendant hydroxyl. Therefore, a more stepwise approach, wherein the C-18/C-19 olefin would first be epoxidized, was investigated (Scheme 2).

Sharpless asymmetric epoxidation[8] of polyprenol **6** smoothly afforded the C-18/C-19 epoxide (+)-**7** in 99% yield with >90% ee based upon Mosher ester analysis.[9] The terminal isopropylidene unit was then chemoselectively protected via dihydroxylation employing the Corey−Zhang ligand (**10**)[6a]

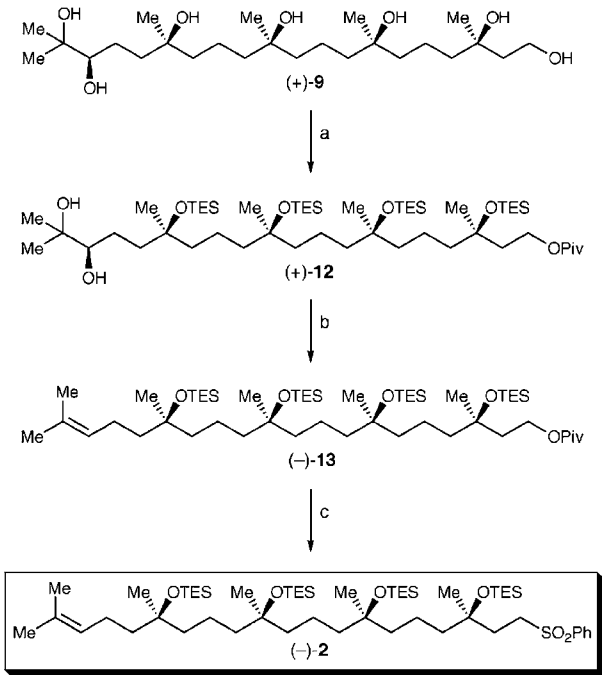
Scheme 2[a]



[a] Reagents and conditions: (a) Ti(O*i*-Pr)$_4$, D-(−)-DIPT, 3 Å MS, cumene hydroperoxide, CH_2Cl_2, −30 °C, 99%. (b) $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, **10** (1.6 mol %), $K_2OsO_4 \cdot 2H_2O$ (1.2 mol %), *t*-BuOH/H_2O (1:1), 0 °C, 61%, 77% BORSM. (c) (1) **11** (1.8 equiv), $Na_2B_4O_7/Na_2EDTA$ buffer, *n*-Bu_4NHSO_4, K_2CO_3, Oxone (5.2 equiv), H_2O, MeCN, DMM, 0 °C; (2) $LiAlH_4$ (12 equiv), 1,4-dioxane, 90 °C, 52% over two steps.

to furnish diol (+)-**8** in good yield with NMR analysis indicating a high degree of diastereoselectivity (dr > 15:1). We next turned our attention to the key epoxidation event. To our delight, employing 1.8 equiv (0.6 equiv/olefin) of catalyst **11**[5a] with a slow delivery (5 h) of aqueous solutions of Oxone and K_2CO_3 via syringe pumps provided the desired tetraepoxide in excellent yield (78%) with the mass recovery after chromatographic purification being ca. 85% of a single stereoisomer. Reductive opening of the four oxiranes with excess $LiAlH_4$ then gave heptaol (+)-**9**. Differentiation of the seven hydroxyls was next accomplished by esterification of the primary hydroxyl (PivCl, DMAP, pyr), followed by benzylidene acetal formation, and silylation of the remaining tertiary hydroxyls (Scheme 3). Hydrogenolysis in the pres-

Scheme 3[a]



[a] Reagents and conditions: (a) (1) PivCl, DMAP, pyr, CH_2Cl_2, −78° C; (2) $PhCH(OMe)_2$, PPTs, DMF; (3) TESOTf, 2,6-lutidine, CH_2Cl_2; (4) $Pd(OH)_2/C$, EtOAc/EtOH (10:1), 58% over four steps. (b) (1) $Pb(OAc)_4$, THF; (2) $(CH_3)_2CHPPh_3I$, *n*-BuLi, THF, 93% over two steps. (c) (1) Dibal-H, CH_2Cl_2, −78 °C; (2) I_2, PPh_3, imidazole, Et_2O/MeCN (3:1); (3) $PhSO_2Na$, DMF, 60 °C, 59% over three steps.

ence of Pearlman's catalyst then furnished diol (+)-**12** in good overall yield (58% overall yield for the four steps). Reintroduction of the terminal isopropylidene was then realized via lead tetraacetate-mediated glycol cleavage,

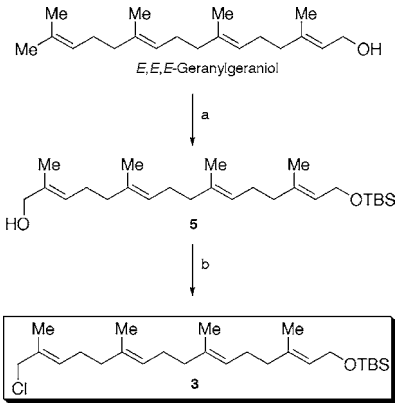
(4) Radetich, B.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 2430.
(5) (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc*. **1997**, *119*, 11224. (c) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 2948. (d) Wang, Z.-X.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 3099. (e) Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 4425. (f) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 7819. (g) Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 8475.

followed by Wittig olefination. The two-step process afforded the desired alkene (−)-**13** in excellent yield (93%).[10]

All that remained to complete the sulfone coupling partner, (−)-**2**, was reductive removal of the pivaloate ester (Dibal-H), followed in turn by conversion of the resulting hydroxyl to the iodide (PPh_3, I_2, imidazole),[11] and S_N2 displacement with the sodium salt of benzenesulfinic acid.

With a reliable route to sulfone (−)-**2** available, we investigated the allylic oxidation of TBS-protected (*E*,*E*,*E*)-geranylgeraniol necessary for the construction of the tetraene coupling partner **3**. After exploring several reaction conditions, the Sharpless catalytic method[12] proved to be the most reliable. However, the desired terminal allylic alcohol **5**[13] could only be obtained in low yield [ca. 10% (Scheme 4)].

Scheme 4 [a]

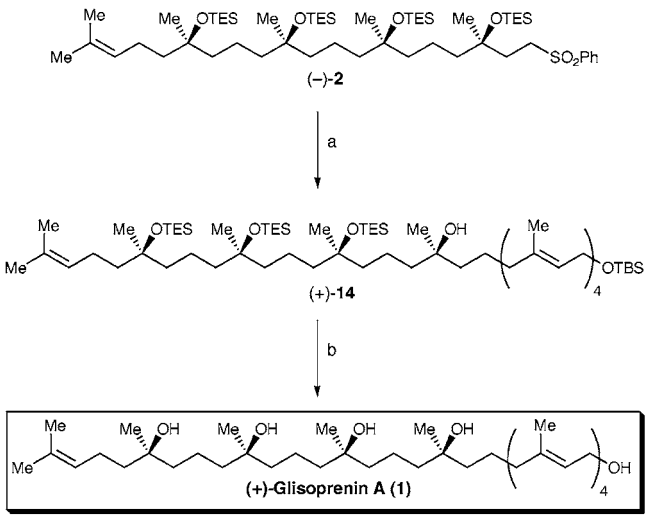


[a] Reagents and conditions: (a) (1) TBSCl, imidazole, DMF; (2) cat. SeO_2, *t*-BuOOH, salicylic acid, CH_2Cl_2, ca. 10% over two steps. (b) MsCl, LiCl, 2,6-lutidine, DMF, 86%.

Chlorination in accordance with the Meyers protocol[14] then provided the allyl chloride **3** in good yield.

With both the sulfone (−)-**2** and chloride **3** in hand, we explored their coupling (Scheme 5). Lithiation of (−)-**2** (*n*-BuLi, 10% HMPA/THF), followed by addition of chloride **3**, gave the desired adduct as a mixture of diastereomeric sulfones in 75% yield [93% based on recovered (−)-**2**],

Scheme 5 [a]



[a] Reagents and conditions: (a) (1) *n*-BuLi, THF, 10% HMPA, then **3**; (2) 5% Na/Hg amalgam, Na_2HPO_4, MeOH/THF, 69% over two steps. (b) TFA, THF/H_2O, 96%.

which underwent reductive removal of the sulfone moiety (Na/Hg amalgam) to furnish (+)-**14** in 92% yield. Acid-mediated global deprotection (TFA, THF/H_2O) then afforded synthetic glisoprenin A.

The synthetic compound was confirmed to be identical to the natural product through the following two sets of NMR experiments. First, the ^1H and ^{13}C NMR spectra (CD_3OD)[15] of the synthetic compound were found to be indistinguishable from those of the natural product. Their identity was further assured from the fact that no signal doubling was detected in the ^1H and ^{13}C NMR spectra of a 2:1 mixture of the synthetic and natural glisoprenin A, thereby demonstrating, at least, that the synthetic and natural compounds possess the same gross structure (Figure 1, panels A−C). Second, the ^{13}C NMR behaviors in the presence of chiral shift reagents were studied; specifically, a 2:1 mixture of the synthetic and natural glisoprenin A was subjected to ^{13}C NMR experiments in C_6D_6−CD_2Cl_2 (v/v 4:1) containing 25 mol % (*R*)- or (*S*)-Pr(tfc)$_3$/OH. Under these conditions, all eight α-carbons were observed as a separate resonance (Figure 1, panel D). Critically, no signal-doubling was detected for any of the eight resonances in the presence of either (*R*)- or (*S*)-Pr(tfc)$_3$, thereby further demonstrating that the synthetic and natural compounds do indeed possess the same absolute configuration at all four tertiary alcoholic centers.

In conclusion, the total synthesis of (+)-glisoprenin A, highlighted by a series of asymmetric oxidations, has been

(6) (a) Corey, E. J.; Zhang, J. *Org. Lett.* **2001**, *3*, 3211. (b) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741.

(7) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodríguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515.

(8) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(9) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

(10) Attempts to reintroduce the terminal isopropylidene earlier in the synthesis, i.e., from (+)-**12** via Corey−Winter olefination, met with limited success.

(11) Garegg, P. J.; Samuelsson B. *J. Chem. Soc., Chem. Commun.* **1979**, 978.

(12) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

(13) Two-dimensional NMR analysis and chemical correlation (i.e., desilylation of **5** afforded the known diol; see: Tago, K. Minami, E.; Masuda, K.; Akiyama, T.; Kogen, H. *Bioorg. Med. Chem.* **2001**, *9*, 1781) were used to confirm the site of oxidation.

(14) Collington, E. W.; Meyer, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

(15) All NMR experiments in the presence of (*R*)- or (*S*)-Pr(tfc)$_3$ were conducted in C_6D_6−CD_2Cl_2 (v/v 4:1). However, in the absence of shift reagent the NMR spectra of both synthetic and natural glisoprenin A in C_6D_6−CD_2Cl_2 (v/v 4:1) proved to be highly variable, presumably due to issues associated with aggregation. Although NMR analysis of a 2:1 mixture of synthetic and natural glisoprenin A did not indicate any signal doubling in C_6D_6−CD_2Cl_2 (v/v 4:1), we felt it prudent to perform the analysis in CD_3OD, a solvent that precludes any aggregation. All spectra taken in CD_3OD are provided in Supporting Information.

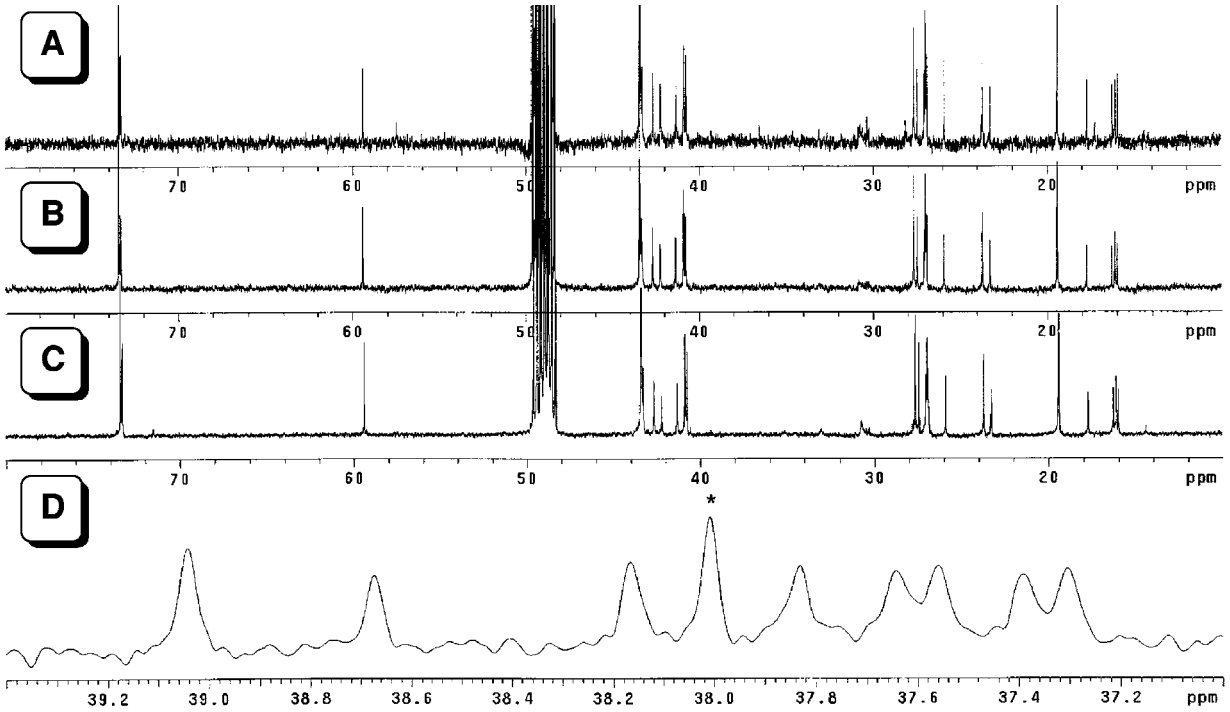


Figure 1. Panel A: 100 MHz ^{13}C NMR of natural (+)-**1** (80−10 ppm, in CD_3OD). Panel B: 100 MHz ^{13}C NMR of a 2:1 mixed sample of synthetic (+)-**1** to natural (+)-**1** (80−10 ppm in CD_3OD). Panel C: 100 MHz ^{13}C NMR of synthetic (+)-**1** (80−10 ppm, in CD_3OD). Panel D: 125 MHz ^{13}C NMR spectra (the α-carbon region) of a 2:1 mixed sample of synthetic (+)-glisoprenin A to natural (+)-glisoprenin A in $C_6D_6-CD_2Cl_2$ (v/v 4:1) containing 25 mol % (*R*)-Pr(tfc)$_3$/OH. The asterisk (*) indicates resonance of the allylic carbon at C-4.

achieved. This work not only confirms the predicted stereostructure of (+)-**1**, but also validates the chiral lanthanide shift approach for determination of absolute configuration.

Acknowledgment. We thank Professor S. Omura, The Kitasato Institute, for a generous gift of natural (+)-glisoprenin A, and we gratefully acknowledge Professor E. J. Corey for a generous gift of ligand **10**. Financial support was provided by the NIH through Grant NS 12108, by Eisai Research Institute, and by a Postdoctoral Fellowship from the American Cancer Society (PF-03-134-01-CDD) to C.M.A.

Supporting Information Available: Spectroscopic and analytical data for compounds **1**, **5**, **7**−**9**, and **12**−**14** and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048059O