Pergamon

Tetrahedron Letters 41 (2000) 8107–8110

TETRAHEDRON LETTERS

Synthesis of the optically active bicyclo[4.3.0]nonane derivative, regarded as the CD ring moiety of 12-oxygenated steroids

Hidemichi Mitome, Hiroaki Miyaoka and Yasuji Yamada*

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received 3 July 2000; revised 16 August 2000; accepted 18 August 2000

Abstract

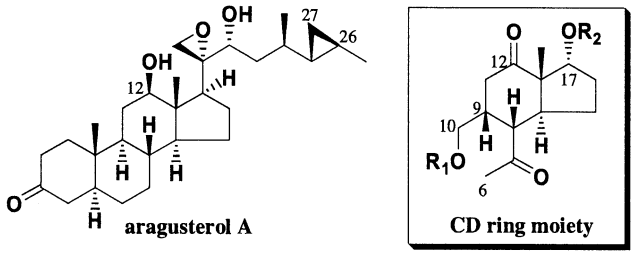
The optically active bicyclo[4.3.0]nonane derivative, considered to be the CD ring moiety of 12-oxygenated steroids was synthesized in the present study, which involved stereo-controlled formation of bicyclo[2.2.2]octane derivative by sequential Michael reaction, formation of tricyclo[5.2.2.$0^{2,6}$]undecane derivative by intramolecular pinacol coupling reaction and the C–C bond cleavage by retro-aldol reaction.

Keywords: steroids and sterols; bicyclic aliphatic compounds; Michael reactions.

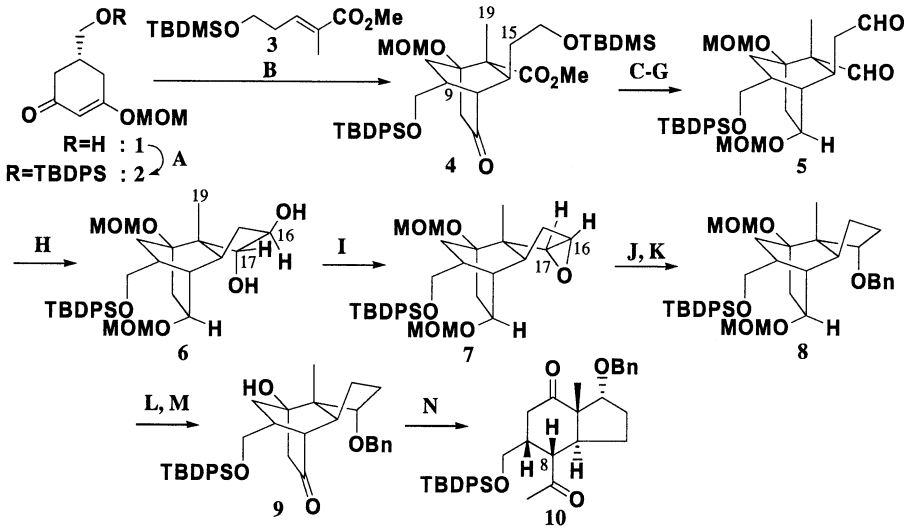
Aragusterols A–H, isolated from an Okinawan marine sponge of the genus *Xestospongia*, are structurally unique antitumor marine steroids, each possessing a 12β-hydroxyl group on the steroidal nucleus and a side chain with a rare 26, 27-cyclo structure.[1] Of these, aragusterols A and C expressed potent antitumor activity toward L1210 leukemia in mice (T/C 220 and 257% at 1.6 mg/kg)[1a,b] and it was demonstrated that the 12-oxygenated functionality plays an important role in the antitumor activity. Aragusterols A–D were previously synthesized through the enantioselective formation of a side chain segment and coupling of a steroidal nucleus segment which was prepared from (+)-hecogenin with this side chain segment.[2] For further detailed pharmacological studies on aragusterols, we planned total synthesis of aragusterols rather than using natural (+)-hecogenin as a starting material. Though a number of steroids have been synthesized, no method for efficient synthesis of the 12-oxygenated steroidal nucleus is reported. In the present study, as the first step of the total synthesis of aragusterols the authors describe synthesis of bicyclo[4.3.0]nonane derivative regarded as the CD ring moiety of aragusterols, which may be corresponded to the key component for the synthesis of the 12-oxygenated steroidal nucleus.

* Corresponding author. Tel: +81 426 76 3046; fax: +81 426 76 3069; e-mail: yamaday@ps.toyaku.ac.jp

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01413-1



In our synthetic studies on natural products, bicyclo[2.2.2]octane derivatives as chiral building blocks have been found to be quite useful for the stereoselective synthesis of substituted cyclohexane derivatives[3] and also applicable to the synthesis of the CD ring moiety of 12-oxygenated steroids. The synthetic strategy of the optically active bicyclo[4.3.0]nonane derivative involved formation of bicyclo[2.2.2]octane derivative **4** by stereoselective sequential Michael reaction, formation of tricyclo[5.2.2.$0^{2,6}$]undecane derivative **6** by intramolecular pinacol coupling reaction, and subsequent cleavage of the C(6)–C(12) bond[4] in **9** by retro-aldol reaction to afford the bicyclo[4.3.0]nonane derivative **10** as shown in Scheme 1.



Scheme 1. *Reagents*: **A**. TBDPSCl, imidazole, quant.; **B**. LDA then **3**, 65%; **C**. $NaBH_4$, 73%; **D**. MOMCl, $^iPr_2NEt$, quant.; **E**. $LiAlH_4$, 96%; **F**. *cat*. PPTS, MeOH, 96%; **G**. PCC, 62%; **H**. SmI_2, THF–HMPA (10:1), 74%; **I**. Ph_3P, DEAD, 91%; **J**. Super-Hydride®, 99%; **K**. NaH, BnBr, 95%; **L**. *B*-bromocatecholborane, 79%; **M**. PCC, 89%; **N**. (1) TMSCl, $ZnCl_2$, Et_3N, 110°C, (2) AcOH–THF–H_2O (2:1:1), two steps, 72%

Optically active alcohol **1**[5] ($[\alpha]_D^{26}$ −94.2 (*c* 0.3, $CHCl_3$), 99% ee), which was obtained by kinetic resolution using lipase-catalyzed enantioselective esterification of (±)-**1**, was transformed into cyclohexenone derivative **2** by protection of the hydroxyl group as TBDPS ether. A kinetic enolate of **2** was treated with α,β-unsaturated ester **3**[6] in THF at room temperature to afford bicyclo[2.2.2]octane derivative **4**, $[\alpha]_D^{27}$ −17.8 (*c* 1.4, $CHCl_3$) as the sole product in 65% yield.[7] The stereochemistry of **4** was determined based on the correlations of H-15 with H-9 and with H-19 in the NOESY spectrum.

Ketoester **4** was converted to dialdehyde **5**, $[\alpha]_D^{28}$ −41.8 (*c* 1.8, $CHCl_3$), in the following five steps: (1) $NaBH_4$ reduction of **4** to afford an alcohol as the sole product,[8] (2) protection of the hydroxyl group as MOM ether, (3) $LiAlH_4$ reduction of ester to give primary alcohol, (4) deprotection of TBDMS ether by PPTS in MeOH and (5) PCC oxidation of two primary hydroxyl groups thus obtained dialdehyde **5.** The formation of cyclopentane corresponding to the D ring of the 12-oxygenated steroidal nucleus was carried out by intramolecular pinacol reaction[9] of **5**. Dialdehyde **5** was treated with SmI_2 in the presence of HMPA at room temperature to afford tricyclo[5.2.2.$0^{2,6}$]undecan derivative **6**, $[\alpha]_D^{27}$ −39.4 (*c* 2.1, $CHCl_3$), as the sole product in 74% yield.[10] The absolute configurations of the newly formed stereocenters in **6** were assigned as 16*S*,17*S* based on the correlation of H-17 with H-19 in the NOESY spectrum and the ^1H–^1H coupling constant ($J=0$ Hz) between H-16 and H-17 in the ^1H NMR spectrum.

Diol **6** was treated with Ph_3P and DEAD to give epoxide **7** in 91% yield.[11] The stereochemistry of this epoxide was determined as 16*R*,17*S* based on the correlation of H-17 with H-19 in the NOESY spectrum. Treatment of **7** with Super-Hydride® provided the corresponding alcohol as the sole product in 99% yield.[12] Regioselectivity in this epoxide-opening reaction may be explained as an attack of hydride ion on the less hindered carbon of the epoxide. The hydroxyl group thus obtained was protected as benzyl ether to give **8** in 95% yield. Deprotection of the MOM ethers[13] of **8** followed by PCC oxidation of the secondary hydroxyl group afforded β-hydroxyketone **9**, $[\alpha]_D^{27}$ −33.4 (*c* 1.2, $CHCl_3$).

Regioselective C–C bond cleavage through retro-aldol reaction was performed by treating **9** with $ZnCl_2$, Et_3N and TMSCl[14] to provide TMS enol-ether of bicyclo[4.3.0]nonane derivative **10**. Subsequent hydrolysis gave the desired compound **10**, $[\alpha]_D^{27}$ −23.3 (*c* 1.3, $CHCl_3$) in two steps (72% yield). When **9** was subjected to retro-aldol reaction with NaH in the presence of 15-crown-5-ether as catalyst,[15] the reaction proceeded smoothly to give the aimed for product in 84% yield. The product, however, was an inseparable mixture of epimers at H-8 (β:α = 2:1).

Bicyclo[4.3.0]nonane derivative **10** is equivalent to the CD ring moiety of 12-oxygenated steroids and has the necessary functional groups for the construction of A and B rings and the side-chain. The total synthesis of aragusterols using this compound as an intermediate is presently being studied.

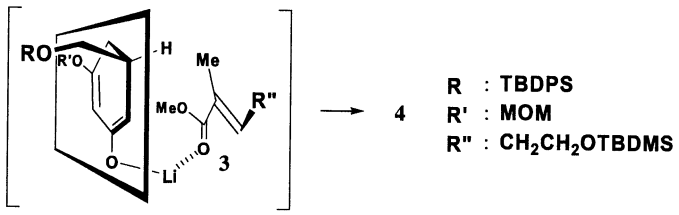
Acknowledgements

This work was supported in part by Grant-in-Aids for Scientific Research (Grant No. 11771398) from the Ministry of Education, Science, Sports and Culture of Japan.

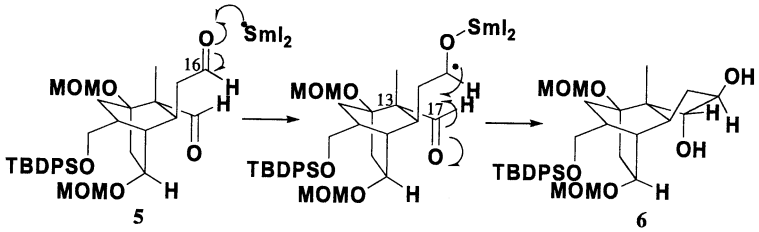
References

1. (a) Iguchi, K.; Fujita, M.; Nagaoka, H.; Mitome, H.; Yamada, Y. *Tetrahedron Lett*. **1993**, *34*, 6277–6280. (b) Shimura, H.; Iguchi, K.; Yamada, Y.; Nakaike, S.; Yamagishi, T.; Matsumoto, K.; Yokoo, C. *Experientia* **1994**, *50*, 134–136. (c) Iguchi, K.; Shimura, H.; Taira, S.; Yokoo, C.; Matsumoto, K.; Yamada, Y. *J. Org. Chem*. **1994**, *59*, 7499–7502. (d) Miyaoka, H.; Shinohara, M.; Shimomura, M.; Mitome, H.; Yano, A.; Iguchi, K.; Yamada, Y. *Tetrahedron* **1997**, *53*, 5403–5412.
2. Mitome, H.; Miyaoka, H.; Nakano, M.; Yamada, Y. *Tetrahedron Lett*. **1995**, *36*, 8231–8234.
3. Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett*. **1996**, *37*, 7107–7110.
4. This numbering is in accordance with that for steroidal skeleton.

5. Miyaoka, H.; Sagawa, S.; Inoue, T.; Nagaoka, H.; Yamada, Y. *Chem. Pharm. Bull.* **1994**, *42*, 405–407.
6. α,β-Unsaturated ester **3** was prepared in two steps (56% yield): (1) PDC oxidation of 3-(*tert*-butyldimethylsilyloxy)-1-propanol, (2) treatment of resulting aldehyde with methyl 2-(triphenylphosphoranylidene)propionate. cf: McDougal, P. G.; Rico, J. G.; Oh, Y.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388–3390.
7. High diastereo-selectivity in reaction of **2** with **3** may be explained based on the transition states shown below. α,β-Unsaturated ester **3** approaches kinetic enolate of **2** from the less hindered side with coordination of the lithium cation of enolate **2** with carbonyl oxygen of **3**.



8. Stereoselective reduction of **4** by $NaBH_4$ may proceed from attack of the hydride ion at the less hindered side of the carbonyl group.
9. (a) Namy, J. E.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765–766. (b) Kan, T.; Matsuda, F.; Yanagiya, M.; Shirahama, H. *Synlett* **1991**, 391–392.
10. This reaction may proceed as follows: (1) one electron reduces the less hindered carbonyl function at C-16 of **5**; (2) resulting radical attacks C-17 through the *anti* conformation comprised of methyl at C-13 and carbonyl oxygen at C-17.



11. Carlock, J. T.; Mack, M. P., *Tetrahedron Lett.* **1978**, 5153–5156.
12. Rao, A. S.; Pakinikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323–2367.
13. Boeckman, R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411–1414.
14. Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808.
15. Miyaoka, H.; Isaji, Y.; Kajiwara, Y.; Kunimune, I.; Yamada, Y. *Tetrahedron Lett.* **1998**, *39*, 6503–6506.