ORGANIC LETTERS

2000
Vol. 2, No. 13
1951−1953

# A Facile Construction of the Quadranoid Skeleton: Application to the Total Synthesis of (±)-Suberosenone

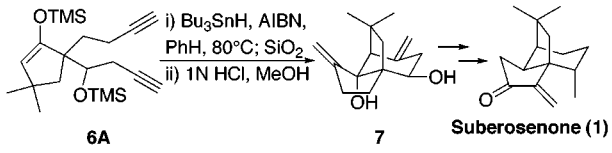
**Hee-Yoon Lee* and Byung Gyu Kim**

*Center for Molecular Design and Synthesis, Department of Chemistry and School of Molecular Science (BK21), Korea Advanced Institute of Science and Technology, Taejon 305-701, Korea*

*leehy@cais.kaist.ac.kr*

**Received May 5, 2000**

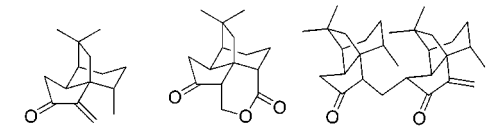
## ABSTRACT




**A tandem free radical cyclization–rearrangement sequence was designed and executed to produce tricyclo[4.3.2.0$^{1,5}$]undecane 7 from cyclopentene 6A in a single operation. The total synthesis of suberosenone was accomplished from 7.**

Recently, Bokesch reported the structures of suberosenone-(**1**),[1] a new cytotoxic sesquiterpene related to quadrone(**2**),[2] and its dimer alertenone (**3**) (Scheme 1).[3] While alertenone

**Scheme 1**




showed significantly low cytotoxicity, suberosenone exhibited potent and differential cytotoxicity toward various cancer cell lines. The contrasting antitumor activity of suberosenone with quadrone led us to search for a facile synthetic route to the core structure of quadranoid compounds.

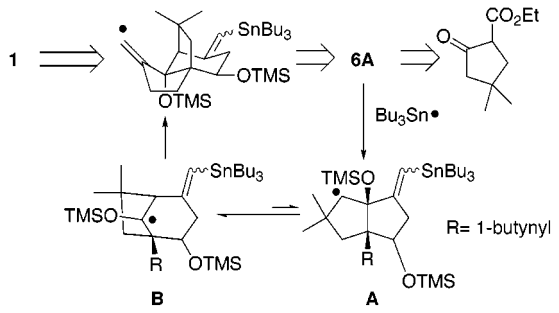
Quadrone has been a focal point for the development of numerous synthetic methodologies and strategies during the 1980s, and several elegant total syntheses[4] and synthetic approaches[5] to quadrone have been reported. However, an SAR study of the antitumor activity of quadrone and its congeners was not extensively explored since most of the synthetic routes did not offer a ready access to the tricyclic core structure of quadrone.[6] A facile construction of the core structure of quadranoids will allow the synthesis of various analogues of quadranoid natural products as well as the total synthesis of natural products themselves.

Our synthetic strategy of suberosenone was based on our recent finding of a novel construction of tricyclo[4.3.2.0$^{1,5}$]-undecane structures.[7] The crucial tandem radical cyclization reaction utilized cyclopropylmethyl radical mediated rearrangement (Scheme 2). The steric congestion of eclipsing

(1) Bokesch, H. R.; McKee, T. C.; Cardellina II, J. H.; Boyd, M. R. *Tetrahedron Lett*. **1996**, *37*, 3259.
(2) Calton, G. J.; Ranier, R. L.; Espenshade, M. A. *J. Antibiot.* **1973**, *31*, 38.
(3) Bokesch, H. R.; Blunt, J. W.; Westergaard, C. K.; Cardellina, J. H., II; Johnson, T. R.; Michael, J. A.; McKee, T. C.; Hollingshead, M. G.; Boyd, M. R. *J. Nat. Prod*. **1999**, *62*, 633.
(4) Ermolenko, M. S.; Pipelier, M. *Tetrahedron Lett*. **1997**, *38*, 5975.
(5) Smith, A. B., III; Konopelski, J. P.; Wexler, B. A.; Prengler, P. A. *J. Am. Chm. Soc*. **1991**, *113*, 3533.
(6) Gordeeva, E. V.; Lushnikov, D. E.; Zefirov, N. S. *Tetrahedron* **1992**, *48*, 3787.
(7) Lee, H. Y.; Kim, B. G. *Book of Abstracts*, 11th ICOS, Amsterdam, The Netherlands; IUPAC & KNCV: Amsterdam, 1996; PO-026.
(8) Clive, D. L. J.; Magnuson, S. R.; Manning, H. W.; Mayhew, D. L. *J. Org. Chem*. **1996**, *61*, 2095.
(9) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc*. **1978**, *100*, 6728.
(10) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107.
(11) Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem*. **1984**, *49*, 1313.
(12) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem*. **1978**, *43*, 2480.

10.1021/ol0060230 CCC: $19.00 
**Published on Web 06/06/2000**

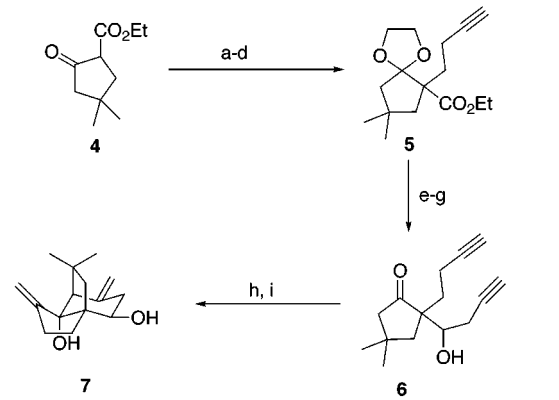
**Scheme 2**




substituents at ring junctions of **A** and the radical stabilizing effect of the oxygen atom of the rearranged intermediate **B** must favor the seemingly less favorable endocyclic intermediate.[8] The second radical cyclization should also drive the overall sequence of reactions toward **B**. Thus, the core skeleton of quadrone and suberosenone would be constructed in a single operation from a cyclopentane ring. This will yield a quick entry into the synthesis of various analogues as well as the total syntheses of quadranoid natural products.

Execution of the above strategy required the preparation of 2,2-disubstituted cyclopentanone **6** (Scheme 3). First, a

**Scheme 3**[a]

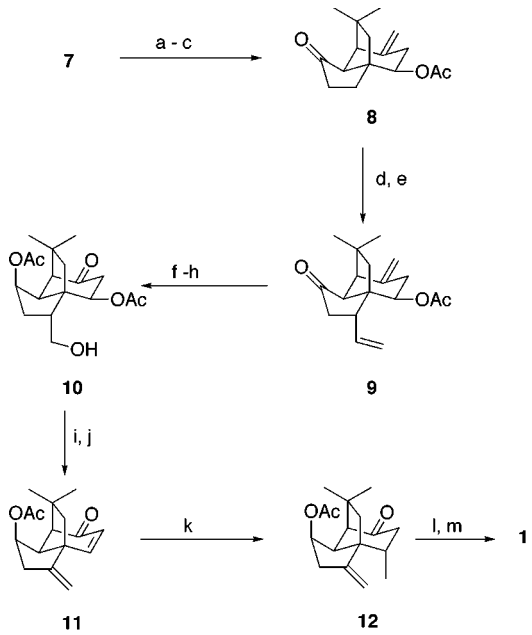



[a] (a) 4-bromo-1-butene (1.5eq), $K_2CO_3$ (3eq), DMF, 0°C, 60%; (b) ethyleneglycol, *p*-TsOH, PhH, quant.; (c) $O_3$, $CH_2Cl_2$, -78°C, then $PPh_3$, 91%; (d) $TMSCHN_2$(1.5eq), LDA (1.5eq), 65%; (e) LAH (1.1eq), $Et_2O$, then DMSO(2eq.), $(COCl)_2$(4eq.), -78°C,then $Et_3N$(5eq.), 0°C, 91%; (f) (3-TMS-2-propynyl)magnesium bromide (1.5eq), $Et_2O$, 91%; (g) TBAF (1.1eq), THF, then *p*-TsOH (0.05eq), acetone/$H_2O$ (10/1), 88%; (h) TMSOTf (2.5eq), $Et_3N$ (3eq), $Et_2O$, 91%; (i) $Bu_3SnH$ (1.2eq), AIBN (0.05eq), PhH, 80°C, then $SiO_2$, then 1N HCl, MeOH, 49%

butynyl chain was introduced onto 4,4-dimethyl-2-carbethoxycyclopentanone[9] in a four-step sequence (anionic alkylation with 3-butenyl bromide, protection of the ketone as ethylene ketal, and ozonolysis followed by acetylene formation using TMS-diazomethane anion[10]) since direct alkylations with 3-butynyl halides or sulfonates were not successful.[11] After the ester of **5** was converted to the corresponding aldehyde ($LiAlH_4$ reduction followed by Swern oxidation[12]), addition of propargyl Grignard reagent produced the alkynol with a good diastereoselectivity (9:1). Chelation of oxygens of the aldehyde and acetal could account for the diastereoselectivity. Desilylation followed by deprotection of the major isomer produced **6**. After trimethylsilyl triflate treatment of **6**, the crucial free radical cyclization reaction was performed under the general reaction conditions for tin hydride mediated enyne cyclization reactions.[13] After destanylation using silica gel, only one regioisomeric product, **7**, was obtained. Since **6** possessed two terminal alkynes, a mixture of regioisomeric products was expected from the nonselective addition of tributyltin radical to the seemingly unbiased alkynes. This unexpected selectivity is presumed to come from the conformational preference of the butynyl chain with a hydroxyl group in **6** toward cycloaddition reaction,[14] since the radical stabilizing effect from a heteroatom could not be large enough to distinguish two terminal alkynes in **6**.

With the tricyclo[4.3.2.$0^{1,5}$]undecane product **7** in hand, the total synthesis of suberosenone was accomplished in a straightforward manner (Scheme 4). Selective ozonolysis of the allylic alcohol of **7**[15] followed by reductive deoxygenation of the tertiary alcohol using $SmI_2$[16] produced **8** after

**Scheme 4**[a]




[a] (a) $O_3$, $CH_2Cl_2$, -78°C, then $PPh_3$, 68%; (b) $SmI_2$ (1.5eq), THF, -78°C, 97%; (c)$Ac_2O$ (5eq), $Et_3N$ (5eq), DMAP (0.1eq), $CH_2Cl_2$, 98%; (d) LHMDS (1.1eq), PhSeCl (1.1eq), THF, -78°C, then $NaIO_4$ (1.5eq), MeOH/$H_2O$ (5/1), 51%; (e) CuCN (0.2eq), vinylmagnesium bromide (1.5eq), $Et_2O$, -78°C, 87%; (f) $NaBH_4$ (1.5eq), MeOH, then $Ac_2O$ (10eq), DMAP (0.1eq), $Et_3N$ (10eq), $CH_2Cl_2$, 95%; (g) $O_3$, $CH_2Cl_2$, -78°C, then $Me_2S$; (h) THF, $NaBH(OAc)_3$ (1.5eq), 80% (for tow steps); (i) *o*-nitrophenylseleno cyanate (1.2eq), $Bu_3P$ (1.2eq), THF; (j) $NaIO_4$ (1.5eq), MeOH/$H_2O$ (5:1), $NaHCO_3$ (5eq), 40°C, 64% (for two steps); (k)CuCN (0.2eq), MeMgBr (2eq), $Et_2O$, -78°C, 88%; (l) i. DIBAL-H (2.5eq), $CH_2Cl_2$, 0°C; ii. *n*-BuLi (10eq), $CS_2$ (10eq), THF, 0°C, then MeI (40eq); iii. $Bu_3SnH$ (2.5eq), AIBN (0.1eq), PhH, 80°C, 51%; (m) $SeO_2$ (0.5eq), *t*-BuOOH (1.2eq), $CH_2Cl_2$, 0°C, then TPAP (0.1eq), NMO (1.5eq), $CH_2Cl_2$, 60%.

protection of the remaining alcohol as the acetate. Then, **8** was converted to the corresponding enone through α−selenation (LHMDS, PhSeCl) followed by a selenoxide elimination reaction.[17] Addition of vinyl cuprate to the enone produced a single isomeric 1,4-addition product, **9**. Approach from the sterically less encumbered bottom face of the C-ring should give complete selectivity. The ketone of **9** was reduced with $NaBH_4$, and the corresponding alcohol was protected as the acetate. The reduction also proceeded with complete stereoselectivity. Ozonolysis of the two remaining olefins to the keto aldehyde followed by the selective reduction of the aldehyde with $NaBH(OAc)_3$[18] produced keto alcohol **10**. At this stage, the primary alcohol was dehydrated to the exocyclic olefin to ensure the stereoselective introduction of the methyl group at C-9. The dehydration was accomplished using the Grieco protocol.[19] During this reaction, the acetate at C-9 was also eliminated to afford enone **11**. Dimethyl cuprate addition produced a single isomeric ketone, **12**. The stereochemistry of the methyl group was confirmed through NOE measurement. Again, steric and stereoelectronic effects offered complete control of the stereochemistry of the methyl group.[20] The total synthesis of suberosenone was completed from **12** by deoxygenation followed by allylic oxidation. Deoxygenation of the ketone and acetate of **12** was accomplished using Barton's radical deoxygenation reaction[21] of the corresponding diol which was prepared by DIBAL-H reduction of **12** to yield volatile 4-deoxysuberosenone. Finally, introduction of a carbonyl group at the C-4 carbon through allylic oxidation of the olefin using $SeO_2$ followed by TPAP oxidation[22] produced suberosenone **1**. Comparison of IR, $^1$H NMR, and $^{13}$C NMR spectral data of synthetic suberosenone with the reported spectral data of natural suberosenone[23] confirmed the structure of **1**.

Thus far, we have demonstrated a facile route to the core skeleton of quadranoids from a cyclopentane ring in a single operation. Accomplishment of the total synthesis of suberosenone also showed the versatility of the current synthetic methodology.

**Acknowledgment.** This work was supported by KOSEF (98-0501-05-01-3). We are grateful to Dr. J. H. Cardellina II and Dr. M. R. Boyd for providing an NMR spectrum of natural suberosenone.

**Supporting Information Available:** Spectral data of **1** and **5**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0060230

(13) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829.
(14) MM2 minimized energy for the conformation of **6** to form the intermediate for the observed product was 1.4 kcal/mol lower than that for the other product.
(15) The chemoselectivity was presumed to result from the steric bias imposed by the *gem*-dimethyl group since the selectivity reversed when the desdimethyl analogue of **7** was subjected to the ozonolysis conditions.
(16) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.
(17) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc*. **1973**, *95*, 5813.
(18) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proc. Int.* **1985**, *17*, 317.
(19) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem*. **1976**, *41*, 1485.
(20) Wender, P. A.; Wolanin, D. J. *J. Org. Chem.* **1985**, *50*, 4418.
(21) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(22) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(23) The $^1$H NMR spectrum of natural suberosenone was superimposable to that of synthetic suberosenone.