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Studies on the Total Synthesis of (−)-CP-263,114

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Alkoxyl radicals have a wide range of applications in organic synthesis due to their remarkable chemical properties in molecular transformation. The present study shows two types of alkoxyl radicals (primary vs tertiary) to selectively undergo dehydrogenation and β-scission to give rise to key structural elements of (−)-CP-263,114 (**1**). By alkoxyl radical transformation followed by installation of the C19-C25 (CP numbering) side chain and the bridged bisacetal unit, the functionalized CP precursor **2** was obtained.

Introduction:

(−)-CP-263,114 (phomoidride B) (**1**), a bioactive fungal metabolite,[1] is of considerable interest to the synthetic chemical community (Figure 1). Fascination with the CP molecule stems from the structural uniqueness as well as the potent inhibitory activity toward *ras*-farnesyl transferase and suqualene synthase, both current targets of medicinal concern. Four successful total syntheses of **1**[2] appear in the literature and new routes to produce this natural product are avidly being sought.[3,4]

We previously reported an enantioselective approach based on alkoxyl radical reactions to a simple core structure of (−)-CP-263,114 (**1**).[5a,6] In this study, the synthesis of the advanced CP precursor **2** was conducted through the following key transformations (Scheme 1): (1) introduction of the oxygen functionality at C26 via primary alkoxyl radical-mediated dehydrogenation (**10** → **11** → **12**), (2) formation of bridgehead double bond via iodo transfer β-scission of a tertiary alkoxyl radical intermediate followed by reduction of iodo ether (**8** → **7** → **5**), and (3) production of the polycyclic caged CP-motif **2** via thioketalization and subsequent bisacetal unit construction (**4** → **3** → **2**).

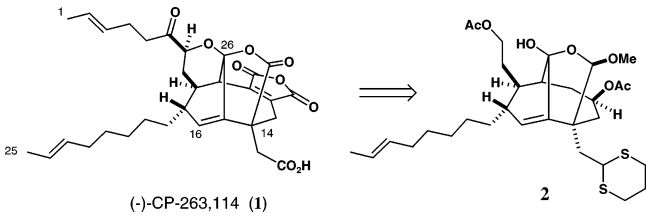

FIGURE 1. Functionalized CP precursor **2**.

Results and Discussion

Alkoxyl radicals are widely used in the synthesis of organic molecules owing to chemical properties that allow useful reactions such as hydrogen abstraction and β-scission.[7,8] Alkoxyl radical reactions thus serve as means for key transformation in the synthesis of various natural products.[9−13] The pathways of these reactions generally depend on the types of alkoxyl radicals generated:

(1) (a) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594−1598. (b) Spencer, P.; Agnelli, F.; Williams, H. J.; Keller, N. P.; Sulikowski, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 420−423. (c) Spencer, P.; Angelli, F.; Sulikowski, G. A. *Org. Lett*. **2001**, *3*, 1443−1445. (d) Sulikowski, G. A.; Angelli, F.; Spencer, P.; Koomen, J. M.; Russell, D. H. *Org. Lett*. **2002**, *3*, 1447−1450.

(2) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1669−1675. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 1676−1678. (c) Nicolaou, K. C.; Jung, J.-K.; Yoon, W. H.; He, Y.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1829−1832. (d) Nicolaou, K. C.; Jung, J.; Yoon, W. H.; Fong, K. C.; Choi, H.-S.; He, Y.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 2183-2189. (e) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; Choi, H.-S. *J. Am. Chem. Soc.* **2002**, *124*, 2190−2201. (f) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Jung, J.; Choi, H.-S.; Yoon, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 2202−2211. (g) Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4509−4511. (h) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424−7425. (i) Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825−7826. (j) Hayashi, Y.; Itoh, T.; Fukuyama, T. *Org. Lett*. **2003**, *5*, 2235−2238.

(3) Selected recent papers from other laboratories; (a) Davies, H. M. L.; Ren, P. D. *Tetrahedron Lett*. **2000**, *41*, 9021−9024. (b) Devaux, J.-F.; O'Neil, S. V.; Guillo, N.; Paquette, L. A. *Collect. Czech. Chem. Commun.* **2000**, 65, 490−510. (c) Crimmins, M. T.; Hauser, E. B. *Org. Lett*. **2000**, *2*, 281−284. (d) Baldwin, J. E.; Adlington, R. M.; Roussi, F.; Bulger, P. G.; Marquez, R.; Mayweg, A. V. W. *Tetrahedron* **2001**, *57*, 7409−7416. (e) Isakovic, L.; Ashenhurst, J. A.; Gleason, J. L. *Org. Lett*. **2001**, *3*, 4189−4192. (f) Toyota, M.; Majo, V. J.; Ihara, M. *Tetrahedron Lett*. **2001**, *42*, 1555−1558. (g) Ohmori, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 755−767. (h) Matsushita, T.; Ashidas, H.; Kimachi, T.; Takemoto, Y. *Chem. Commun*. **2002**, 814−815. (i) Sulikowski, G. A.; Liu, W.; Agnelli, F.; Corbett, R. M.; Luo, Z.; Hershberger, S. J. *Org. Lett*. **2002**, *4*, 1451−1454. (j) Armstrong, A.; Critchley, T. J.; Gourdel-Martin, M.-E.; Kelsey, R. D.; Mortlock, A. A. *Tetrahedron Lett*. **2002**, *43*, 6027−6030. (k) Spiegel, D. A.; Njardarson, J. T.; Wood, J. L. *Tetrahedron* **2002**, *58*, 6545−6554. (l) Bio, M. M.; Leighton, J. L. *J. Org. Chem.* **2003**, *68*, 1693−1700. (m) Banwell, M. G.; Coster, M. J.; Edwards, A. J.; Voegtle, M. *Aust. J. Chem.* **2003**, *56*, 577−583. (n) Clive, D. L. J.; Sgarbi, P. W. M.; He, X.; Sun, S.; Zhang, J.; Ou, L. *Can. J. Chem.* **2003**, *81*, 811−824.

(4) For reviews, see: (a) Diederichsen, U. *Nachr. Chem. Tech. Lab*. **1999**, *47*, 1423−1427. (b) Starr, J. T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1415−1412. (c) Hepworth, D. *Chem. Ind.* (*London*) **2000**, *2*, 59−65. (d) Nicolaou, K. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002,** *41*, 2678−2720. (e) Spiegel, D. A.; Njardarson, J. T.; McDonald, I. M.; Wood, J. L. *Chem. Rev.* **2003**, *103*, 2691−2727.

(5) (a) Yoshimitsu, T.; Yanagisawa, S.; Nagaoka, H. *Org. Lett.* **2000**, *2*, 3751−3754. (b) Yoshimitsu, T.; Yanagiya, M.; Nagaoka, H. *Tetrahedron Lett*. **1999**, *40*, 5215−5218.

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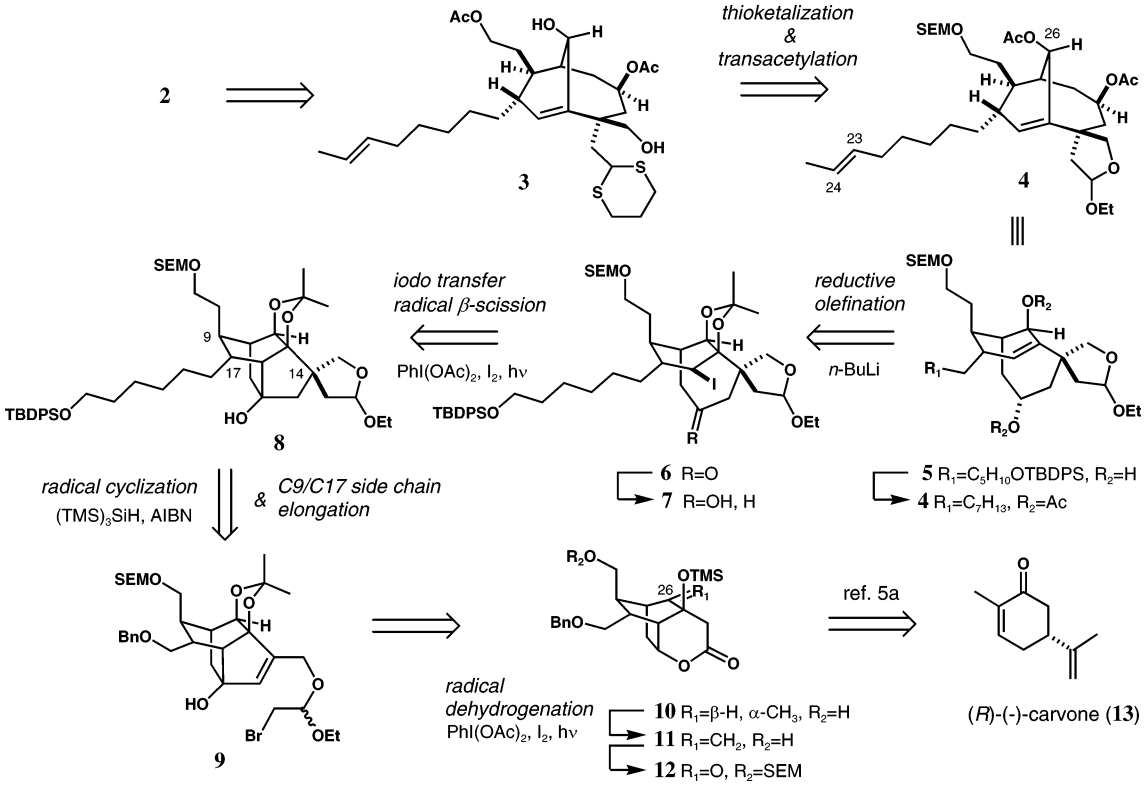
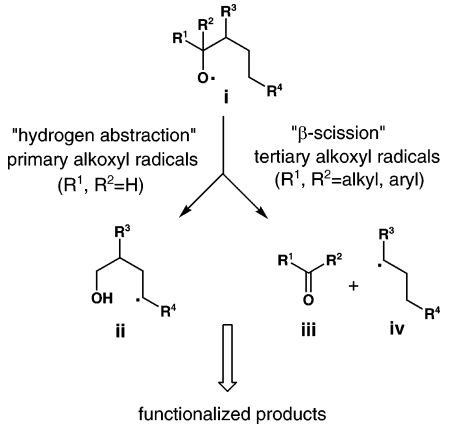
SCHEME 1. Synthetic Approach Based on Alkoxyl Radical Reactions to (−)-CP-263,114 (1)



primary alkoxyl radicals are susceptible to hydrogen abstraction (**i** → **ii**) whereas tertiary radicals favor β-scission (**i** → **iii** + **iv**) (Scheme 2).

Primary Alkoxyl Radical Dehydrogenation of 10. Primary alcohol **10**,[5a] prepared in 7 steps from (−)-carvone (**13**) with an overall yield of 27%, was subjected to alkoxyl radical-mediated dehydrogenation

SCHEME 2. Pathways of Alkoxyl Radical Reactions



(Scheme 3).[14] A mixture of alcohol **10**, diacetoxyiodobenzene (DIB),[15,16] and iodine in dichloromethane at 0 °C was irradiated with visible light (150 W tungsten lamp) to produce the desired olefin **11** (29%), iodo ether **14** (21%),

(6) Synthetic radical chemistry from this laboratory: novel radical α-C−H hydroxyalkylation of THF and its application to acetogenin synthesis: (a) Yoshimitsu, T.; Tsunoda, M.; Nagaoka, H. *Chem. Commun.* **1999**, 1745−1746. (b) Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Org. Chem.* **2003**, *68*, 625−627. (c) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2003**, *68*, 7548−7550. (d) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 1993−1998. Atom transfer radical annulation approach to paclitaxel: (e) Yoshimitsu, T.; Nakajima, H.; Nagaoka, H. *Tetrahedron Lett.* **2002**, *43*, 8587−8590.

(7) For comprehensive reviews of synthetic radical chemistry, see: (a) Giese, B. *Radicals in Organic Synthesis*: *Formation of Carbon−Carbon Bonds*; Pergamon Press: Oxford, UK, 1986. (b) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: New York, 1992. (c) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley & Sons: Paris, France, 1995. (d) Neumann, W. P. *Synthesis* **1987**, 665−683. (e) Curran, D. P. *Synthesis*. **1988**, 417−439 (Part 1), 489−513 (Part 2). (f) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237−1286. (g) Togo, H. *Chemistry in Organic Free Radicals*; Kodansha: Tokyo, Japan, 2001. (h) Renaud, P.; Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001. (i) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224−2248.

(8) (a) Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **2002**, *43*, 1821−1824. (b) Boto, A.; Hernández, D.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2003**, *68*, 5310−5319. (c) Antunes, C. S. A.; Bietti, M.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* **2004**, *69*, 5281−5289.

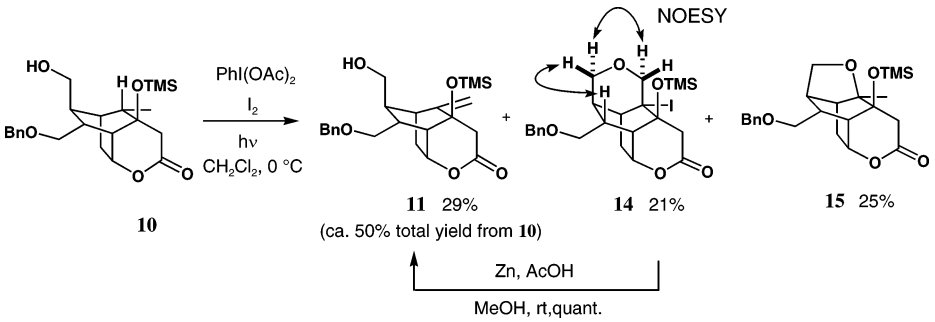
(9) A recent account of alkoxyl radical reactions: Hartung, J.; Gottwald, T.; Spehar, K. *Synthesis* **2002**, 1469−1489.

(10) Reviews of alkoxyl radical fragmentation: (a) Suárez, E.; Rodriguez, M. S. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 440−454. (b) Zhang, W. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 234−245. (c) Yet, L. *Tetrahedron* **1999**, *55*, 9349−9403. (d) Nishida, A.; Nishida, M. *Rev. Heteroatom. Chem.* **1997**, *17*, 287−311.

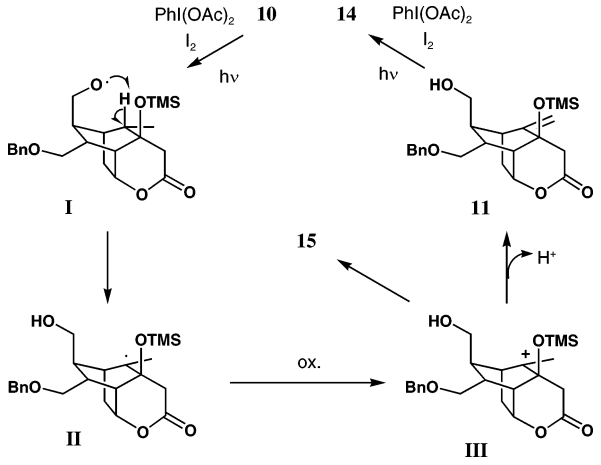
(11) Application of alkoxyl radical β-scission in natural product synthesis, for recent instances, see: (a) Boto, A.; Hernández, R.; Montoya, A.; Suárez, A. *Tetrahedron Lett.* **2004**, *45*, 1559−1563. (b) Fuhshuku, K.; Tomita, M.; Sugai, T. *Tetrahedron Lett.* **2004**, *45*, 1763−1767. (c) Deng, Y.; Snyder, J. K. *J. Org. Chem*. **2002**, *67*, 2864−2873. (d) Weavers, R. T. *J. Org. Chem.* **2001**, *66*, 6453−6461. (e) Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576−4577. (f) Mehta, G.; Mohal, N. *Tetrahedron Lett.* **1999**, *40*, 5791−5794. (g) Rigby, J. H.; Warshakoon, N. C.; Payen, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 8237−8245.

(12) Reviews for alkoxyl radical hydrogen abstraction: (a) Cekovic, Z. *Tetrahedron* **2003**, *59*, 8073−8090. (b) Feray, L.; Kuznetsov, N.; Renaud, P. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 246−278. Review containing a brief discussion on this topic: (c) Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94−103.

SCHEME 3. Alkoxyl Radical Dehydrogenation of Primary Alcohol 10



SCHEME 4. Plausible Mechanism of Radical Dehydrogenation



and ether **15** (25%). Reduction of iodo ether **14** with zinc-acetic acid in methanol provided olefin **11** quantitatively, thereby producing olefin **11** in ca. 50% overall yield from **10**. The six-membered ring structure of iodo ether **14** was unambiguously determined by NOE analysis.

A plausible mechanism for the radical dehydrogenation is shown in Scheme 4. A six-membered cyclic transition state, in which the δ-hydrogen, most accessible from the primary alkoxyl radical center of **I**, is abstracted, would provide carbon-centered radical **II**. Carbon radical **II** subsequently becomes, with oxidation, carbenium ion intermediate **III**, deprotonation of which produces olefin **11**. The cyclization of **III** affords cyclic ether **15**. Iodo ether **14** has been found to be produced from **11** via a photolytic radical pathway rather than an ionic pathway, since formation of **14** from **11** is significantly accelerated by visible light irradiation. This type of radical dehydrogenation[17] may be useful for the regioselective functionalization of unreactive C−H bonds.[18]

Synthesis of Bromo Acetal 9. Bromo acetal **9**, required for the construction of the C14 quaternary center of the CP molecule, was prepared as shown in Scheme 5. Thus, olefin **11** was first transformed into trimethylsilylethoxymethyl (SEM) ether **16**, which was subjected to ozonolysis at −78 °C to afford ketone **12** in 83% yield. Reduction of **12** with $Zn(BH_4)_2$ in ether at 0 °C proceeded stereoselectively from the concave site to provide β-alcohol which, by deprotection of the trimethylsilyl (TMS) group with tetrabutylammonium fluoride (TBAF) followed by ketalization with 2,2-dimethoxypropane in the presence of PPTS, gave acetonide **17** in 80% overall yield. Allylation of **17** and subsequent one-carbon degradation delivered alcohol **19**, which then underwent Grieco olefination[19] to provide vinyl lactone **20** in high yield. Lactone **20** was reduced with LAH in refluxing 1,4-dioxane to give diol, which was selectively converted to monosilyl ether **21** in 87% overall yield. Oxidation of the secondary hydroxyl group in **21** with catalytic TPAP[20] in the presence of 4-methylmorpholine *N*-oxide provided ketone **22** in 93% yield. Ozonolysis of **22** followed by stereoselective intramolecular pinacol coupling of the resulting keto aldehyde efficiently gave diol **23**. Diol **23** was then treated with 1,1′-carbonyldiimidazole and DMAP in THF to afford cyclic carbonate **24** which, by deprotection of the TBS group with TBAF, gave alcohol **25** in 98% yield. Oxidation of **25** with Dess−Martin reagent[21] resulted in spontaneous β-elimination of the carbonate group to provide α,β-unsaturated aldehyde **26** in 95% yield. Selective 1,2-reduction of **26** was successfully carried out with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ to provide alcohol **27**,[22] while DIBAL was found

(13) For recent reports of alkoxyl radical hydrogen abstraction in natural product synthesis, see: (a) Barrero, A. F.; Oltra, J. E.; Alvarez, M.; Rosales, A. *J. Org. Chem.* **2002**, *67*, 5461−5469. (b) Barrero, A. F.; Oltra, J. E.; Alvarez, M. *Tetrahedron Lett.* **2000**, *41*, 7639−7643. (c) Chatgilialoglu, C.; Gimisis, T.; Spada, G. P. *Chem.-Eur. J.* **1999**, 2866−2876. (d) Allen, P. A.; Brimble, M. A.; Prabaharan, H. *Synlett* **1999**, 295−298. (e) Petrovic, G.; Saicic, R. N.; Cekovic, Z. *Synlett* **1999**, 635−637.

(14) A recent impressive instance of alkane functionalization with diacetoxyiodobenzene-I_2, see: Barluenga, J.; González-Bobes, F.; González, J. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2556−2558.

(15) Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1984**, *25*, 1953−1956. Also, see ref 10a.

(16) Reviews for organohypervalent iodine compounds in radical and related reactions: (a) Togo, H.; Katohgi, M. *Synlett* **2001**, 565−581. (b) Ochiai, M. In *Chemistry of Hypervalent Compounds*; Akiba, K., Ed.; VCH Publishers: New York, 1999; Chapter 13, pp 359−387. (c) Zhdankin, V.; Stang, P. J. *Chem. Rev*. **2002**, *102*, 2523−2584. (d) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, CA, 1997. (e) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409−458. (f) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271−1287. (g) *Hypervalent Iodine Chemistry*; Topics in Current Chemistry 224; Wirth, T., Ed.; Springer-Verlag: Berlin, Germany, 2003.

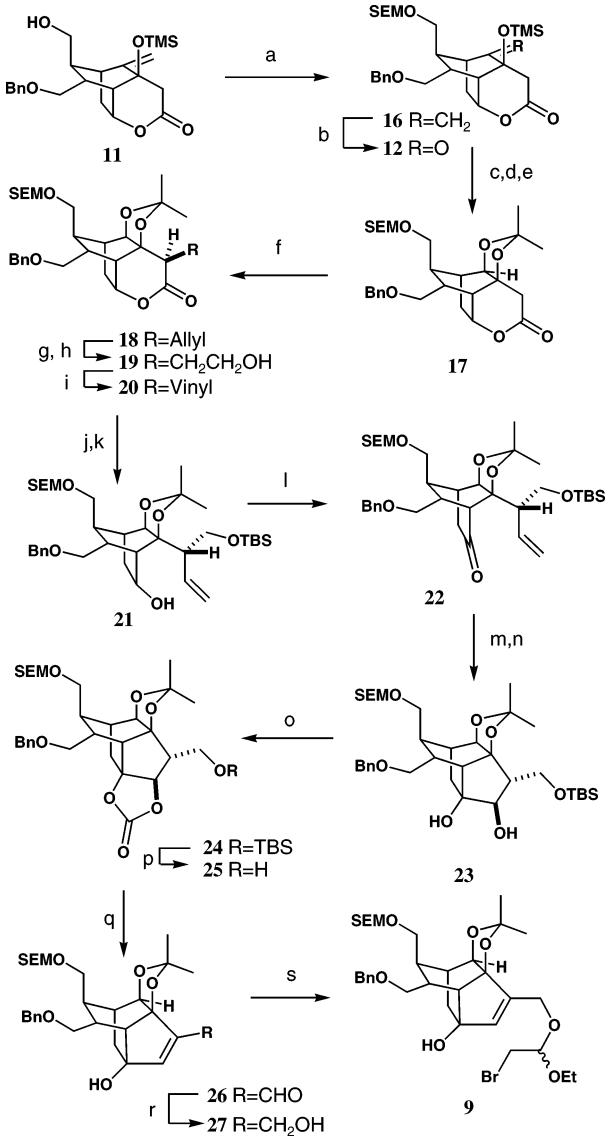
(17) (a) Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 3251−3262. (b) Breslow, R. *Chemtracts* **1988**, *1*, 333−348. (c) Jung, M. E.; Johnson, T. W. *J. Am. Chem. Soc.* **1997**, *119*, 12412−12413. For reviews of the remote radical functionalization, see: (d) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501−526. (e) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095−7129.

(18) Metal-mediated dehydrogenation in natural product synthesis, for instance, see: (a) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc*. **2002**, *122*, 6900−6903. (b) Johnson, J. A.; Sames, D. *J. Am. Chem. Soc*. **2000**, *122*, 6321−6322.

(19) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485−1486.

(20) (a) Griffith, W. P. *Chem Soc. Rev.* **1992**, 179−185. (b) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13−19.

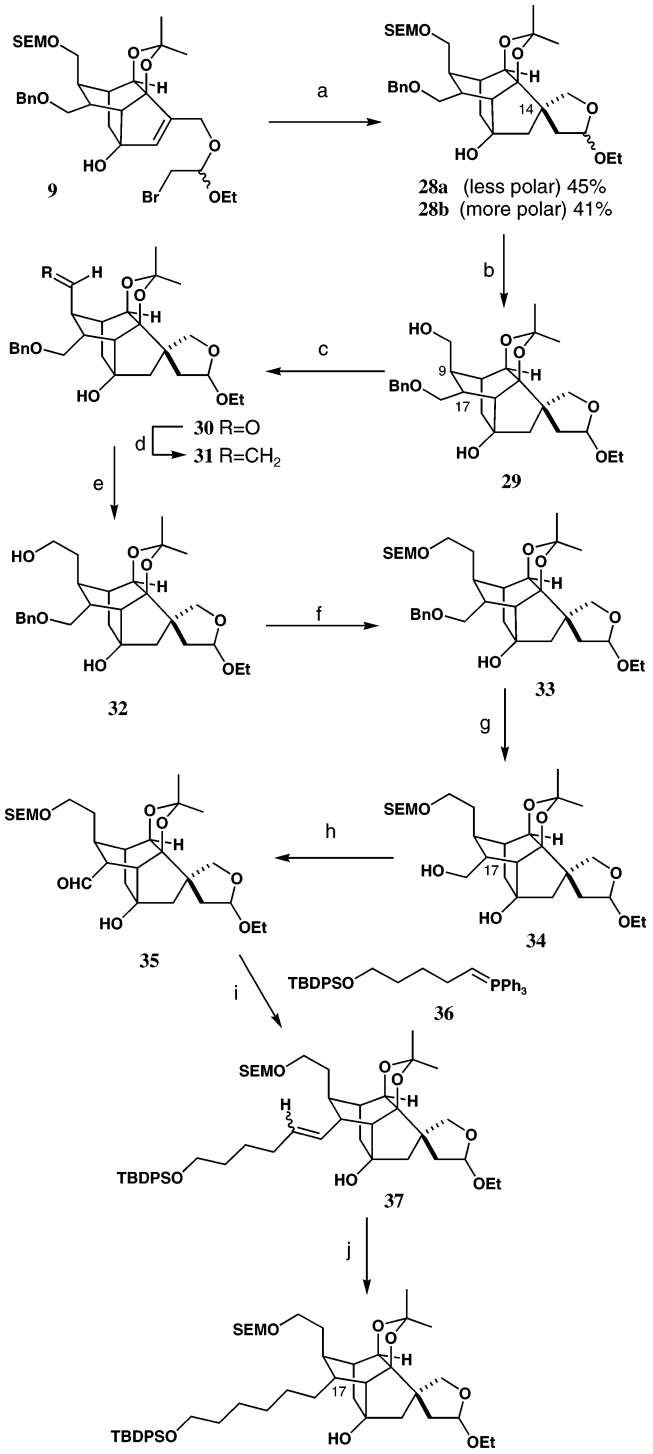
SCHEME 5. Synthesis of Bromo Acetal 9[a]



[a] Reagents and conditions: (a) SEMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 86%; (b) O_3, CH_2Cl_2, then Ph_3P, −78 °C to rt, 83%; (c) $Zn(BH_4)_2$, Et_2O, 0 °C; (d) TBAF, THF, 0 °C; (e) 2,2-dimethoxypropane, PPTS, acetone, CH_2Cl_2, rt, 80%, 3 steps; (f) LiHMDS, allylbromide, HMPA, THF, −78 °C, 85%; (g) O_3, CH_2Cl_2, then Ph_3P, −78 °C to rt; (h) $NaBH_4$, MeOH, rt, 95%, 2 steps; (i) *o*-$O_2NC_6H_4SeCN$, *n*-Bu_3P, THF, −78 to −40 °C, then H_2O_2, THF, 0 °C to rt, 88%; (j) LAH, 1,4-dioxane, reflux; (k) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 87%, 2 steps; (l) TPAP, NMO, MeCN, rt, 93%; (m) O_3, CH_2Cl_2, then Ph_3P, −78 °C to rt, 97%; (n) SmI_2, HMPA, THF, −40 °C to 0 °C, 91%; (o) 1,1′-carbonyldiimidazole, DMAP, THF, rt, 93%; (p) TBAF, THF, rt, 98%; (q) Dess−Martin periodinane, CH_2Cl_2, rt, 95%; (r) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 90%; (s) $ZnCl_2$, 2-bromo-1,1-diethoxyethane, CH_2Cl_2, 0 °C, 77%.

unsuitable for this reduction owing to concomitant formation of a 1,4-reduction byproduct. Alcohol **27** was then treated with bromoacetaldehyde diethyl acetal in the presence of zinc chloride to give an inseparable diastereomeric mixture of acetal **9** in 77% yield.

SCHEME 6. Synthesis of Tertiary Alcohol 8[a]



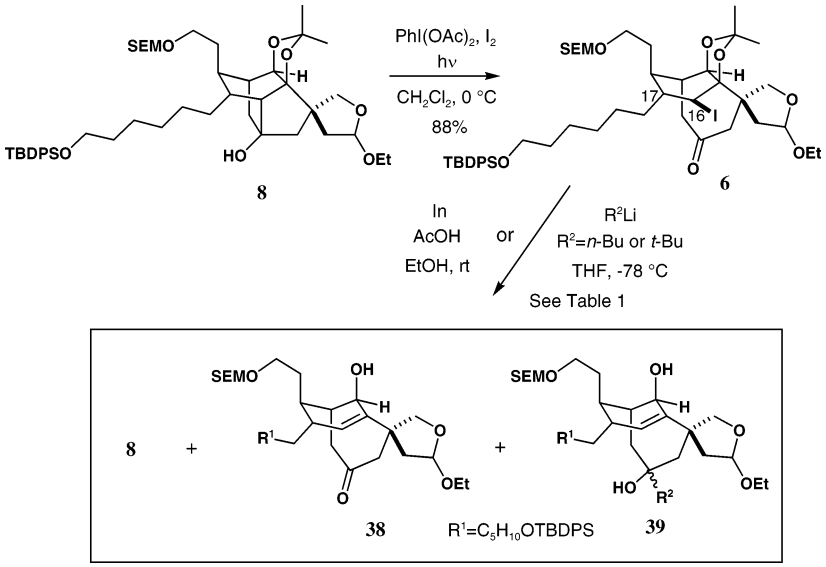
[a] Reagents and conditions: (a) $(TMS)_3SiH$, AIBN, benzene, reflux, **28a** (45%), **28b** (41%); (b) CsF, DMF, 130 °C, 91% from **28a**; (c) Dess−Martin periodinane, CH_2Cl_2, rt, 91%; (d) $Ph_3P{=}CH_2$, THF, 0 °C, 92%; (e) dicyclohexylborane, THF, then NaOH, H_2O_2, 0 °C to rt, 92%; (f) SEMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 93%; (g) $Pd(OH)_2$−C, H_2, EtOAc, rt, 98%; (h) Dess−Martin periodinane, CH_2Cl_2, rt, 91%; (i) **36**, THF, 0 °C to rt, 94%; (j) Pd−C, H_2, EtOAc, rt, 95%.

Synthesis of Tertiary Alcohol 8. With this bromo acetal **9**, the quaternary stereogenic center at C14 was

(21) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (c) Ireland, R. E.; Liu, L. J. *J. Org. Chem.* **1993**, *58*, 2899−2899. (d) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552. (e) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.

(22) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.

SCHEME 7. Alkoxyl Radical β-Scission of Tertiary Alcohol 8 and Olefination of Iodo Ether 6



constructed by radical cyclization (Scheme 6).[23] Thus the treatment of **9** with $(TMS)_3SiH$[24,25] and AIBN led to the formation of cyclized compounds **28a** and **28b**, which could be easily separated by silica gel chromatography, in 86% combined yield (**28a**:**28b** ca. 1:1).[26] The present process is superior to that reported earlier,[5a] which involves acetalization of **27** with ethylvinyl ether and NBS followed by radical cyclization with tributyltinhydride, in terms of higher overall yield (66 vs 49%) and less toxicity of the reagents. For elongation of the side chains at C9 and C17, SEM ether **28a** was first deprotected with cesium fluoride in heating DMF[27] to provide alcohol **29** in 91% yield. Dess−Martin oxidation of **29** afforded aldehyde **30**, and subsequent Wittig olefination gave olefin **31** (92%). Hydroboration/oxidation of **31** provided alcohol **32** whose primary hydroxyl group was protected as SEM ether to afford **33** in 93% yield. Debenzylation of **33** under hydrogenation condition followed by oxidation gave aldehyde **35** in good yield. Wittig olefination of aldehyde **35** with phosphorane **36** provided olefin **37** (94%), which was then subjected to catalytic hydrogenation to furnish alcohol **8** in 95% yield.

Tertiary Alkoxyl Radical β-Scission and Subsequent Bridgehead Olefin Construction. With the acquisition of the intermediate **8**, β-scission of a tertiary alkoxyl radical and subsequent reductive olefination were pursued so as to produce the bridgehead double bond, a characteristic of the CP structure (Scheme 7). Tertiary alcohol **8** was thus treated with DIB and iodine under the same conditions as for the radical dehydrogenation of compound **10** to give the desired keto-iodide **6** as a single diastereomer in 88% yield. The stereochemistry associated with C16 in keto iodide **6** was assigned as (*S*) on the basis of the coupling constant (J_{H16-17} = 12.5 Hz). It should be noted that a complex mixture was obtained in the alkoxyl radical β-scission of alcohol **40** possessing alkenyl substituent probably owing to interference of the reactive olefin moiety with the reagents (Scheme 8).

SCHEME 8. Alkoxyl Radical β-Scission of Tertiary Alcohol 40 Possessing Alkenyl Substituent

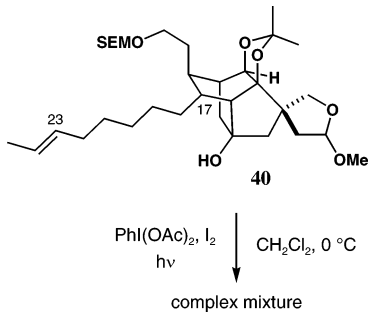


TABLE 1. Olefination of Iodo Ether 6

entry	conditions	products (%)[a]
1	In, AcOH, EtOH, rt	**38** (38), **8** (50)
2	*n*-BuLi, THF, −78 °C	**38** (43), recovered **6** (53)[b]
3	*t*-BuLi, THF, −78 °C	**38** (29), recovered **6** (52)[b]

[a] Isolated yields. [b] Accompanied by small amounts of adduct **39** and cyclized **8**.

The next task was to reduce the iodo ether functionality so as to furnish the bridgehead double bond. Reductive olefination of **6** with indium metal[28] in the presence of acetic acid in ethanol, however, gave olefin **38** in only moderate yield (ca. 40%) due to competitive cyclization leading to the isotwistane compound **8** (50%) (Table 1; entry 1). The desired olefin **38** could be obtained by using *n*-BuLi or *t*-BuLi as the transmetalation reagent,[29] but careful experimental operations were required to sup-

(23) (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564−5566. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741−3742. For more recent instances, see: (c) Clive, D. L. J.; Yu, M.; Sannigrahi, M. *J. Org. Chem.* **2004**, *69*, 4116−4125.

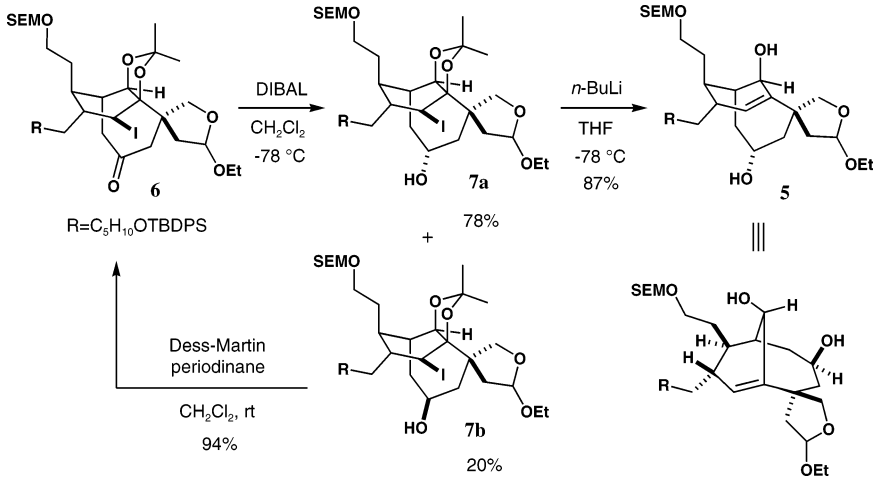
(24) (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194. (b) Chatgilialoglu, C.; Ferreri, C.; Gimisis, T. *The Chemistry of Organic Silicon Compounds*; John Wiley & Sons: New York, 1998; Vol. 2, Chapter 25.

(25) For development of silicon reagents for radical reactions, see: (a) Yamazaki, O.; Yamaguchi, K.; Yokoyama, M.; Togo, H. *J. Org. Chem.* **2000**, *65*, 5440−5442. (b) Sugi, M.; Togo, H. *Tetrahedron* **2002**, *58*, 3171−3175 and references therein.

(26) The stereochemistries associated with the ethyl acetal center in each of compounds **28a** and **28b** have not been determined but we have confirmed that common intermediate **3** in Scheme 10 was similarly obtained from each isomer.

(27) Suzuki, K.; Matsumoto, T.; Tomooka, K.; Matsumoto, K. Tsuchihashi, G. *Chem. Lett.* **1987**, 113−116.

SCHEME 9. Olefination of Iodo Ether 7a



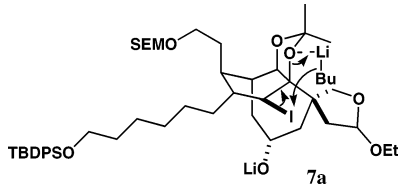
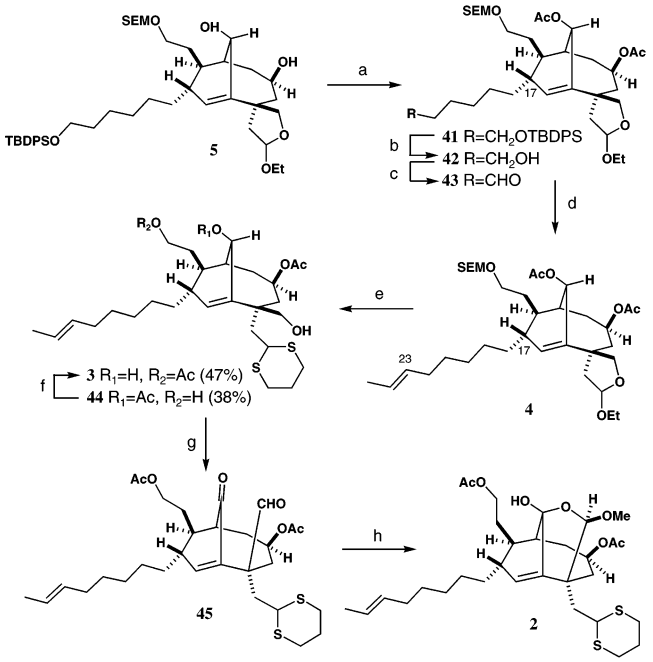


FIGURE 2. Plausible mechanism of olefination of **7a** with *n*-BuLi.

press the nucleophilic addition of the alkyllithium reagents to the carbonyl group of the substrate (Table 1; entries 2 and 3): though the reaction was quenched so that the starting iodo ether **6** remained, detectable byproducts such as reagent-adduct **39** and cyclized compound **8** were produced. These undesired reactions were prevented completely on using alcohol **7a** prepared by reduction of ketone **6** with DIBAL (98% yield, **7a**:**7b** ca. 4:1) (Scheme 9). Major alcohol **7a**[30] was thus treated with *n*-BuLi in THF at −78 °C to provide the expected olefin **5** in 87% yield. *β*-Isomer **7b** was converted to ketone **6**, which could be recycled in the reductive olefination. Although the olefination of **7a** takes place via the poor orbital overlap in the transition state in which the iodine atom at C16 is situated syn to the oxygen functionality at C15, the coordination of the acetal oxygen to lithium cation followed by the butyl anion transfer to iodine atom may facilitate the efficient olefination of compound **7a** (Figure 2).[29a]

Synthesis of CP-Precursor 2. The stage was now set for transforming compound **5** into polycyclic CP-motif

SCHEME 10 [a] **Synthesis of CP-Precursor 2**



[a] Reagents and Conditions: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 99%; (b) TBAF, AcOH, THF, rt, 92%; (c) Dess−Martin periodinane, CH_2Cl_2, rt, 91%; (d) $CrCl_2$, CH_3CHI_2, THF, rt, 92%; (e) 1,3-propanedithiol, concentrated HCl, CH_2Cl_2, rt, **3** (47%), **44** (38%); (f) 1,3-propanedithiol, concentrated HCl, CH_2Cl_2, rt, 73%; (g) Dess−Martin periodinane, CH_2Cl_2, rt,; (h) PPTS, MeOH, rt, 74%, 2 steps.

2 (Scheme 10). Acetylation of **5** followed by deprotection of the *tert*-butyldiphenylsilyl (TBDPS) group of **41** with TBAF produced alcohol **42** in 91% overall yield. Oxidation of **42** with Dess−Martin periodinane and subsequent olefination under the Takai condition[31] resulted in the formation of olefin **4** in 84% overall yield.[32] Sequential transformation of **4** into **3**, involving cyclic thioketal formation, SEM deprotection, and intramolecular transacetylation, was found to proceed in one pot: diacetate **4** was treated with propanedithiol in a two-phase mixture

(28) Reviews for indium chemistry in organic synthesis: (a) Cintas, P. *Synlett* **1995**, 1087−1096. (b) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149−11176. (c) Ranu, B. *Eur. J. Org. Chem.* **2000**, 2347−2356. (d) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015−3019. (e) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633−655. (f) Miyabe, H.; Naito, T. *Org. Biomol. Chem.* **2004**, *2*, 1267−1270. (g) Ueda, M. *Yakugaku Zasshi* **2004**, *124*, 311−319. (h) Nair, V.; Ros. S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959−1982.

(29) (a) Maeda, K.; Shinokubo, H.; Ohshima, K.; Utimoto, K. *J. Org. Chem.* **1996**, *61*, 2262−2263. (b) Ireland, R. E.; Habich, D.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3271−3278. (c) Wender, P. A.; Keenan, R. M.; Lee, H. Y. *J. Am. Chem. Soc.* **1987**, *109*, 4390−4392.

(30) We initially assumed the stereochemistry of the newly generated hydroxyl group of the major alcohol **7a** to be *β* since the hydride attack seemed most likely to occur from the convex site of ketone **6**. The stereochemistry at C12 in compound **7a**, however, was later found to be α as shown in Figure 3 by NOESY analysis of the final compound **2**.

(31) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951−953. Also, see ref 2g.

(32) A trace of *Z*-isomer of olefin **4** was also formed.

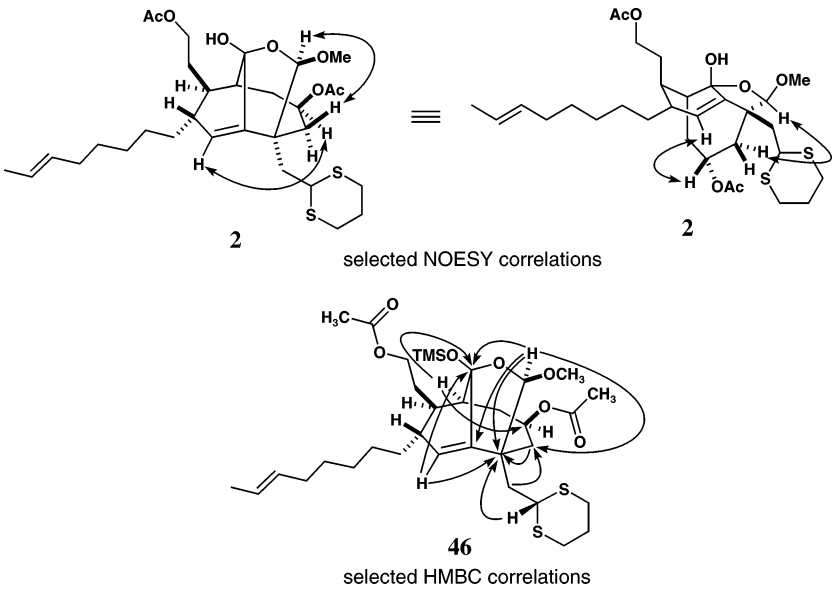


FIGURE 3. Selected NOESY and HMBC interactions in compound **2** and TMS derivative **46**.

of concentrated hydrochloric acid and dichloromethane to provide **3** (47%) along with **44** (38%). Isomeric acetate **44** was converted to the desired **3** in good yield under the same acidic conditions. Dess−Martin oxidation of diol **3** afforded enone **45**, which proved somewhat unstable. Compound **45** was therefore subjected, without purification, to methyl acetal formation with PPTS in methanol to furnish the CP-precursor **2** in 74% overall yield. The structure of **2** was confirmed by inspection of NOESY interactions in **2** and HMBC correlations in TMS derivative **46** (Figure 3).

In conclusion, fully functionalized polycyclic compound **2**, an advanced precursor for the total synthesis of (−)-CP-263,114 (**1**), was obtained in optically pure form.[33] This study demonstrates the distinct chemical behavior of primary and tertiary alkoxyl radicals leading to hydrogen abstraction (**10** → **11**) and β-scission (**8** → **6**) that enable the introduction of the key structural elements of the CP molecule and the usefulness of these radicals in the synthesis of complex molecules. The alkoxyl radical dehydrogenation is particularly useful for the regioselective functionalization of unreactive C−H bonds, and the β-scission used in combination with the reduction of the resulting iodo ether functionality provides a new means for the synthesis of functionalized olefins. Using the said precursor in possession, studies toward accomplishing the total synthesis of (−)-CP-263,114 (**1**) are presently underway.

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Supporting Information Available: Full experimental details, spectroscopic and analytical data, and $^{1}H/^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(33) The present synthesis consists of a total of 40 steps from lactone **10** with an overall yield of ca. 0.45%. The overall yield was calculated on the basis of the combined yield of **2** obtained from both **28a** and **28b** although the route from **28a** to **3** appears only in this paper.