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Application of α-Alkoxy Bridgehead Radical for Coupling of Oxygenated Carbocycles

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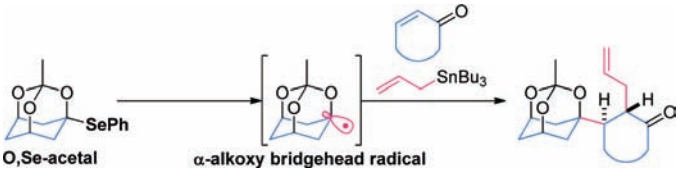
ABSTRACT



A new coupling methodology for assembly of highly oxygenated carbocycles was developed. An α-alkoxy bridgehead radical was employed as the key reactive intermediate due to its potent reactivity, minimum steric interaction, and predestined stereochemical outcome. The radical of the trioxadamantane structure, generated from the O,Se-acetal, was reacted with electron-deficient cyclic olefins of various ring sizes. Intermolecular formation of sterically congested linkages between two tetrasubstituted carbons and application of the method to a three-component coupling were two significant achievements.

Terpenoids constitute one of the largest classes of secondary metabolites in nature.[1] The various carbocyclic structures are often multiply fused and decorated by various oxygen functionalities. These structural elements not only diversify architectural complexity but also impart distinct biological functions to the terpenoids. For instance, the diterpenoids phorbol[2] and trigohownin A[3] share the 5/7/6-fused ring skeleton (Scheme 1) but differ mainly in their surrounding alkoxy functional groups and consequently in their activities, that is, the 12,13-diester of phorbol is a highly effective cocarcinogen, whereas trigohownin A exhibits strong cytotoxic activity. Synthetic chemists have been drawn to terpenoids primarily due to such structural and biological uniqueness.[4,5]

The multiple rings with many alkoxy functionalities present a formidable synthetic challenge. Although considerable efforts have been devoted to their syntheses, there is no universal methodology to construct hindered C−C bonds within the highly oxidized ring structures. In this context, we were interested in developing a new general strategy for construction of the ring connection motif, which is embedded in numerous oxidized terpenoids including phorbol and trigohownin A (see C−C bonds highlighted in red in Scheme 1). Here we report a radical-mediated stereoselective coupling method to form linkages between tertiary alkoxy carbons and tertiary/quaternary carbons. The present intermolecular reaction enables facile assembly of the two oxygenated ring structures into complex bicycles in a single step by applying either two- or three-component coupling protocols.

Construction of sterically congested C−C bonds between the two rings necessitates judicious design of potently

(1) (a) *Comprehensive Natural Products Chemistry*; Barton, Sir D., Nakanishi, K., Meth-Cohn, O., Eds.; Elsevier: Oxford, 1999; Vol. 2. (b) Dewik, P. M. *Medicinal Natural Products, A Biosynthetic Approach*, Third ed.; Wiley: West Sussex, 2009.

(2) Evans, F. J., Ed. *Naturally Occuring Phorbol Esters*; CRC Press: Boca Raton, FL, 1986.

(3) Dong, S.-H.; Zhang, C.-R.; Xu, C.-H.; Ding, J.; Yue, J.-M. *J. Nat. Prod.* **2011**, *74*, 1255–1261. For a review, see: Liao, S.-G.; Chen, H.-D.; Yue, J.-M. *Chem. Rev.* **2009**, *109*, 1092–1140.

(4) Wender reported total synthesis of phorbol and other structurally related compounds. Phorbol: (a) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D., Jr.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957–8958. (b) Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956–4958. (c) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897–7898. Prostratin and DPP:(d) Wender, P. A.; Kee, J.-M.; Warrington, J. M. *Science* **2008**, *320*, 649–652. Resiniferatoxin: (e) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976–12977.

(5) For reviews on synthesis of complex terpenoids, see: (a) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44–122. (b) Maimone, T. J.; Baran, P. S. *Nat. Chem. Biol.* **2007**, *3*, 396–407.

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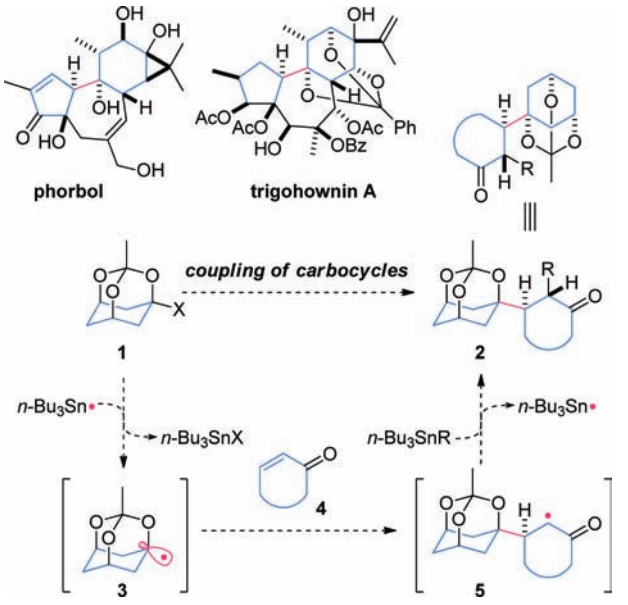
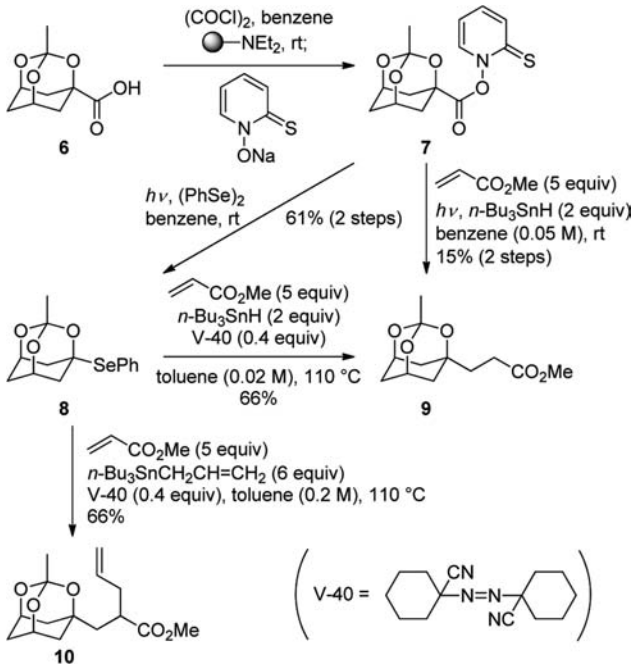
Scheme 1. Plan for Application of α-Alkoxy Bridgehead Radical to Construct a Linkage between Two Oxygenated Carbocycles



Scheme 2. Generation and Subsequent C−C bond Formation of α-Alkoxy Bridgehead Radical



reactive species with minimum steric interactions. The key reactive intermediate selected for this purpose is α-alkoxy bridgehead radical **3** (Scheme 1).[6] Homolytic cleavage of the C-X bond of 2,4,10-trioxadamantane orthoester **1** would generate radical **3**, which subsequently adds to cyclic α,β-unsaturated ketone **4**, resulting in the carbon-chain attached bicycle **2** after introduction of the R group to **5**. Bridgehead radical **3** was considered to be advantageous over the corresponding acyclic α-alkoxy radical due to its high reactivity and predestined stereochemical outcome. Namely, the radical of **3** is spacially more exposed and thus more reactive, and the O-based stereocenter is fixed by the cage structure throughout the reaction. Despite these potentially useful properties, bridgehead radicals with α-oxygen atoms have not been systematically studied[7] in comparison to their carbocyclic counterparts (e.g., adamantyl radical[8]).[9]

To evaluate the synthetic potential of α-alkoxy bridgehead radicals, generation of **3** and subsequent addition were first investigated (Scheme 2). Two radical precursors **7** and **8** were prepared from carboxylic acid **6**.[10] Conversion of **6** into the acid chloride using $(COCl)_2$ and a polymer-bound amine[11,12] was followed by addition of the sodium salt of *N*-hydroxypyridine-2-thione to yield Barton ester **7**.[13] Photoirradiation of **7** in turn induced generation of radical **3** at room temperature, which was immediately trapped by $(PhSe)_2$ to afford O,Se-acetal **8** in 61% yield.[14] In contrast to this successful SePh introduction, the photoinduced carbon extension from **7** in the presence of methyl acrylate and *n*-Bu_3SnH resulted in decomposition of **7** and low yielding formation of **9** (15%).[15] On the other hand, O,Se-acetal **8** gave **9** in much higher yield (66%) when treated

(6) For a review on bridgehead radicals, see: Walton, J. C. *Chem. Soc. Rev.* **1992**, 105–112.

(7) (a) Büch, G.; Wüest, H. *J. Org. Chem.* **1979**, *44*, 546–549. (b) Hatakeyama, S.; Kawamura, M.; Takano, S. *J. Am. Chem. Soc.* **1994**, *116*, 4081–4082.

(8) Ohno, M.; Ishizaki, K.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 1285–1288 and references cited therein.

(9) For representative examples on application of carbocyclic bridgehead radicals to synthetic studies on natural products, see: (a) Kraus, G. A.; Andersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, *34*, 1741–1744. (b) Kraus, G. A.; Su, Q. *Synlett* **1994**, 237–237. (c) Kraus, G. A.; Siclovan, T. M.; Watson, B. *Synlett* **1995**, 201–202. (d) Chatgilialoglu, C.; Ferreri, C.; Ballestri, M. *Tetrahedron Lett.* **1996**, *37*, 6387–6390. (e) Kim, S.; Cheong, J. H. *Synlett* **1997**, 947–949.

(10) Compound **6** was synthesized in six steps from the literature known (1*r*,3*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)cyclohexanol. Carda, M.; Van der Eycken, J.; Vanderwalle, M. *Tetrahedron: Asymmetry* **1990**, *1*, 17–20. See Supporting Information for details.

(11) Dong, C.-G.; Henderson, J. A.; Kaburagi, Y.; Sasaki, T.; Kim, D.-S.; Kim, J.-T.; Urabe, D.; Guo, H.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15642–15646.

(12) Acid chloride formation using Et_3N was unsuccessful due to lability of **7** to aqueous workup.

(13) (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun* **1983**, 939–941. For reviews on Barton ester, see: (b) Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675–684. (c) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413–1432. (d) Saraiva, M. F.; Couri, M. R. C.; Hyaric, M. L.; de Almeida, M. V. *Tetrahedron* **2009**, *65*, 3563–3572.

(14) Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron Lett.* **1984**, *25*, 5777–5780.

(15) The low yield appeared to originate from chemical instability of the activated ester moiety of **7** upon the radical reaction with methyl acrylate.

(16) For application of O,Se-acetals for intermolecular radical reactions, see: (a) Abel, S.; Linker, T.; Giese, B. *Synlett* **1991**, 171–172. (b) Nishiyama, Y.; Yamamoto, H.; Nakata, S.; Ishii, Y. *Chem. Lett.* **1993**, 841–844. (c) SanMartin, R.; Tavassoli, B.; Walsh, K. E.; Walter, D. S.; Gallagher, T. *Org. Lett.* **2000**, *2*, 4051–4054. (d) Abe, H.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **2001**, *123*, 11870–11882. (e) Liu, Y.; Gallagher, T. *Org. Lett.* **2004**, *6*, 2445–2448. (f) Woodward, H.; Smith, N.; Gallagher, T. *Synlett* **2010**, 869–872. For a review, see: (g) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700–717.

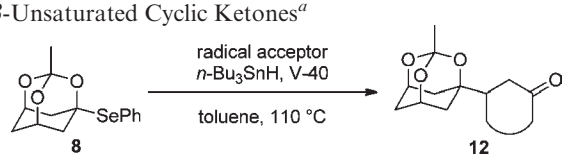
with methyl acrylate, *n*-Bu_3SnH, and V-40 [1,1′-azobis-(cyclohexane-1-carbonitrile)] at 110 °C in toluene.[16] The results clearly demonstrated the superiority of **8** over **7** as a precursor to radical **3** for C−C bond formation.

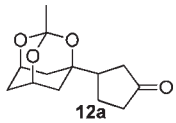
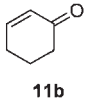
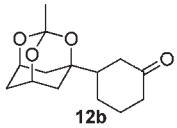
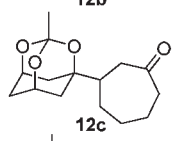
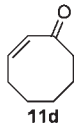
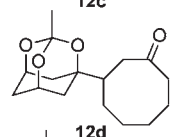
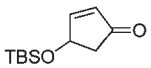
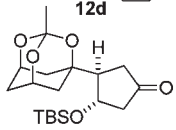
Furthermore, a three-component coupling was realized from O,Se-acetal **8** (Scheme 2).[17] Application of methyl acrylate, allyltributyltin and V-40 to **8** in toluene at 110 °C afforded the branched carboskeleton **10** in 66% yield. Formation of **9** and **10** as major products confirmed that the reaction of **8** followed the scenario envisioned in Scheme 1. Specifically, the reactions of the two pivotal radical species were properly orchestrated. The radical **3** generated from **8** preferred electron-deficient methyl acrylate over the tin reagent, then the resultant electron-deficient α-carbonyl radical reacted with *n*-Bu_3SnH or *n*$Bu_3SnCH_2CH{=}CH_2$ in the presence of methyl acrylate to produce the desired adduct **9** or **10**. Selective addition of α-alkoxy radical **3** to the electrophilic unsaturated bond also confirmed its expected nucleophilic character.[18]

With the establishment of an efficient procedure for radical formation and addition, efforts turned toward the development of a coupling method to form linkages between two carbocyclic structures. Despite the increased steric hindrance, α,β-unsaturated ketones **11** of the five- to eight-membered rings functioned efficiently as radical acceptors (Table 1). In these reactions, a syringe pump was used for slow addition of *n*-Bu_3SnH and V-40 into the toluene solution, and under these optimized conditions the yields of the adducts were effectively maximized by suppressing the undesired reduction of radical **3**. Accordingly, direct attachment of the cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone structures (entries 1−4) to the bridgehead position were achieved to generate **12a**, **12b**, **12c**, and **12d** in 77, 56, 26, and 45% yields, respectively. The radical addition to the oxygenated cyclopentenone derivative **11e** proceeded selectively from the opposite face of the TBSO group, giving rise to **12e** as a single diastereoisomer (entry 5). Thus, we attained intermolecular bond formation between tetrasubstituted and trisubstituted carbons.

The α-alkoxy bridgehead radical technology was next extended to the three-component coupling reaction (Table 2). Treatment of cyclopentenone **11a** and cyclohexenone **11b** with allyltributyltin and V-40 in toluene at 110 °C resulted in formation of 2,3-*trans* disubstituted cycloalkanones **13a** and **13b** in 75% and 32% yields, respectively, both as single diastereoisomers (entries 1 and 2). Moreover, 2,3-*trans*-3,4-*trans*-trisubstituted cyclopentanone **13e** was exclusively produced from **11e** in 77% yield (entry 3), demonstrating that the preexisting stereochemistry of **11e** influenced the selective introduction of the two new stereocenters of **13e**. Consequently, the three-component coupling generated in a single step the complex

Table 1. Coupling between α-Alkoxy Bridgehead Radical and α,β-Unsaturated Cyclic Ketones[a]



entry	radical acceptor	product	yield
1	 **11a**	 **12a**	77%
2	 **11b**	 **12b**	56%
3	 **11c**	 **12c**	26%
4	 **11d**	 **12d**	45%
5	 **11e**	 **12e**	65%[b]

[a] Reaction conditions: **8** (1 equiv), **11** (5 equiv), *n*-Bu_3SnH (6 equiv), V-40 (0.4 equiv), toluene (0.02 M), 110 °C. *n*-Bu_3SnH and V-40 (0.2 equiv) were added by syringe pump over 3 h, and the reaction mixture was stirred for additional 1 h. [b] Compound **12e** was obtained as a single diastereoisomer.

molecule **13e** that corresponds to the bicyclic ring skeleton of trigohownin A (Scheme 1). The stereochemistry of cyclohexanone **13b** was established by X-ray crystallography (Figure 1), and stereochemistry of cyclopentanones **13a** and **13e** was confirmed by NOE experiments on derivatized compounds (See Supporting Information for details).

To further expand the scope of the reaction, we investigated the possibility of constructing two contiguous tetrasubstituted carbons via the intermolecular radical reaction (Table 3). Cycloalkylidenemalononitriles **14a**−**d** were designed as the appropriate radical acceptors, because of the highly electrophilic nature of the exocyclic olefins and the low steric influence of the cyano groups.[19,20] Significantly, radical coupling of **8** with five-, six-, seven-, and eight-membered ring substrates **14a**−**d** all proceeded under the same conditions as those of Table 1, delivering **15a**−**d** in 54, 72, 57, and

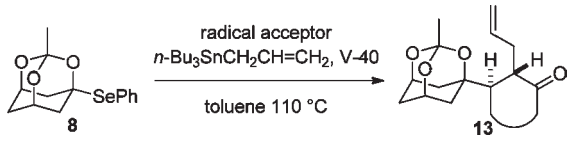
(17) For examples on three-component radical coupling, see: (a) Toru, T.; Watanabe, Y.; Tsusaka, M.; Gautam, R. K.; Tazawa, K.; Bakouetila, M.; Yoneda, T.; Ueno, Y. *Tetrahedron Lett.* **1992**, *33*, 4037–4040. (b) Keck, G. E.; Kordik, C. P. *Tetrahedron Lett.* **1993**, *34*, 6875–6876.

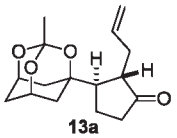
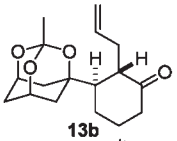
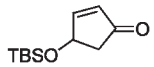
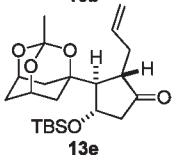
(18) The reaction between **8** and electron rich ethyl vinyl ether in the presence of *n*-Bu_3SnH and V-40 failed to generate the carbon-chain extended product. This also supported the nucleophilic property of radical **3**.

(19) (a) Russell, G. A.; Chen, P.; Yao, C.-F.; Kim, B. H. *J. Am. Chem. Soc.* **1995**, *117*, 5967–5972. (b) Cardarelli, A. M.; Fagnoni, M.; Mella, M.; Albini, A. *J. Org. Chem.* **2001**, *66*, 7320–7327.

(20) Cycloalkylidenemalononitrile **12a**−**d** were synthesized according to the literature procedure. Góra, M.; Kozik, B.; Jamrozy, K.; Luczyński, M. K.; Brzuzan, P.; Woźny, M. *Green Chem.* **2009**, *11*, 863–867.

Table 2. Three-Component Coupling of α-Alkoxy Bridgehead Radical[a]



entry	radical acceptor	product	yield
1	 **11a**	 **13a**	75%[b]
2	 **11b**	 **13b**	32%[b,c]
3	 **11e**	 **13e**	77%[b]

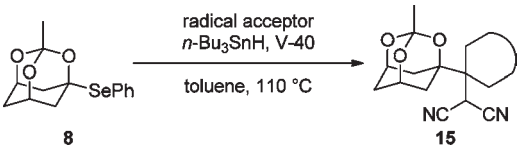
[a] Reaction conditions: **8** (1 equiv), **11** (5 equiv), *n*-Bu_3SnCH_2CH=CH_2 (6 equiv), V-40 (0.4 equiv), toluene (0.2 M), 110 °C, 8 h. [b] Compounds **13a,b,e** were obtained as single diastereoisomers. [c] Compoud **8** was recovered in 15% yield.

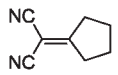
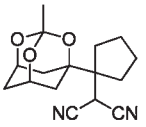
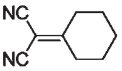
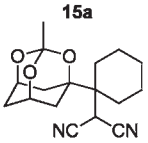
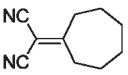
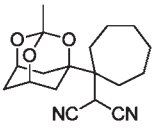
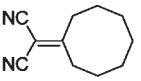
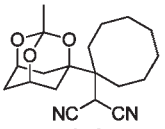
Figure 1. X-ray crystallographic analysis of compound **13b**.

27% yields, respectively. These data demonstrated the power and versatility of the bridgehead radical strategy even for formation of the most sterically demanding bonds.

In summary, we devised a new simple and general methodology for connecting oxygenated carbocycles by utilizing an α-alkoxy bridgehead radical as the key reactive intermediate. The method was applied to the single-step assembly of a variety of highly complex bicycles with simultaneous formation of sterically cumbersome linkages. Furthermore, the two new C−C bonds were produced in a stereocontrolled manner via a three-component

Table 3. Coupling between α-Alkoxy Bridgehead Radical and Cycloalkylidenemalononitriles[a]



entry	radical acceptor	product	yield
1	 **14a**	 **15a**	54%
2	 **14b**	 **15b**	72%
3	 **14c**	 **15c**	57%
4	 **14d**	 **15d**	27%

[a] Reaction conditions: **8** (1 equiv), **14** (5 equiv), *n*-Bu_3SnH (6 equiv), V-40 (0.4 equiv), toluene (0.02 M), 110 °C. *n*-Bu_3SnH and V-40 (0.2 equiv) were added by syringe pump over 3 h, and the reaction mixture was stirred for additional 1 h.

coupling protocol. Because of the ubiquity of the oxidized ring connection motif in terpenoids, many more applications of the present strategy in natural product synthesis are likely. Further transformations from the obtained materials[21] and implementation of the developed strategy into syntheses of oxygenated terpenoids are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of all newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) For examples of chemoselective transformation of orthoesters to the corresponding acetals to liberate specific hydroxy groups, see: (a) Gilbert, I. H.; Holmes, A. B. *Tetrahedron Lett.* **1990**, *31*, 2633–2634. (b) Gilbert, I. H.; Holmes, A. B.; Pestchanker, M. J.; Young, R. C. *Carbohydr. Res.* **1992**, *234*, 117–130. (c) Yeh, S.-M.; Lee, G. H.; Wang, Y.; Luh, T.-Y. *J. Org. Chem.* **1997**, *62*, 8315–8318.