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Two Approaches to Diverting the Course of a Free-Radical Cyclization: Application of Cyclopropylcarbinyl Radical Fragmentations and Allenes as Radical Acceptors†

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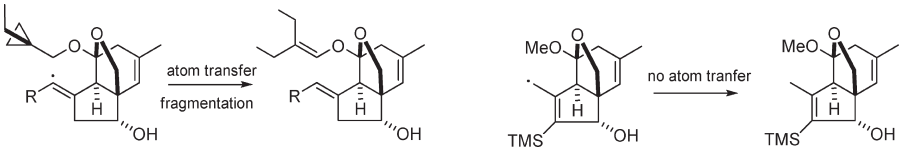
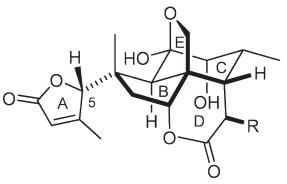
Received August 26, 2009



Free radical cyclization of **4** and **7** gave the expected cyclization-reduction products (**5** and **8**) along with considerable amounts of products derived from a cyclization−atom transfer−secondary cyclization process (**6** and **9**). Two approaches to avoiding these unexpected products were explored. Use of a cyclopropylcarbinyl fragmentation avoided the secondary cyclization reaction (**25** or **43** → **26** or **44**), whereas use of an allene as a radical acceptor avoided the atom-transfer reaction altogether (**49** → **52**).

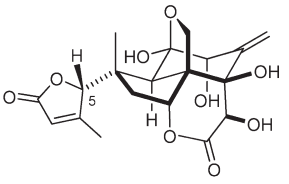
Introduction

The use of free-radical cyclizations in complex target-oriented synthesis has become commonplace during the last 30−40 years.[1] Once in a while, however, a free-radical process rears its head and causes unanticipated problems.[2] This paper describes several such problems, encountered during the course of our attempt to develop a free-radical cyclization route to several C_{19} quassinoids (**1**−**3**), along with some solutions to those problems.[3]



1 R = H (5*R*)-polyandrane

2 R = OH (5*R*)-polyandrol



3 (eurylactone B)

We had planned to use a free-radical cyclization of bromide **4** to *trans*-perhydroindan **5** as a key step in our approach to the polyandranes.[4,5] We had not anticipated that a hydrogen atom transfer−radical cyclization sequence would intervene and thus were caught off guard when treatment of **4** with tri-*n*-butyltin hydride provided **6** in

† This paper is dedicated to the memory of Peter Wagner (1938−2009).

(1) For a synthesis of azadirachtin using an allene as the a radical acceptor, see: Ley, S. V.; Abad-Somovilla, A.; Anderson, J. C.; Ayats, C.; Banteli, R.; Beckmann, E.; Boyer, A.; Brasca, M. G.; Brice, A.; Broughton, H. B.; Burke, B. J.; Cleator, E.; Craig, D.; Denholm, A. A.; Denton, R. M.; Durand-Reville, T.; Gobbi, L. B.; Bobel, M.; Gray, B. L.; Grossmann, R. B.; Gutteridge, C. E.; Hahn, N.; Harding, S. L.; Jennens, D. C.; Jennens, L.; Lovell, P. J.; Lovell, H. J.; de la Puente, M. L.; Kolb, H. C.; Koot, W.-J.; Maslen, S. L.; McCusker, C. F.; Mattes, A.; Pape, A. R.; Pinto, A.; Santafianos, D.; Scott, J. S.; Smith, S. C.; Somers, A. Q.; Spilling, C. D.; Stelzer, F.; Toogood, P. L.; Turner, R. M.; Veitch, G. E.; Wood, A.; Zumbrunn, C. *Chem.—Eur. J.* **2008**, *14*, 10683–10704. For a review of radical cyclizations, see: Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301–856.

(2) For a radical cyclization−atom transfer−radical cyclization sequence related to that encountered in this work, see: Clive, D. L. J.; Khodabocus, A.; Cantin, M.; Tao, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1755–1757.

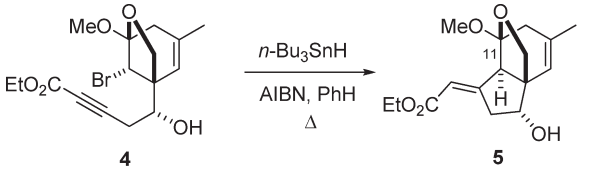
(3) For lead references on the structures and/or synthesis of polyandranes, see: Walker, D. P.; Grieco, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 9891–9892. For compound **1**, see: Aono, H.; Koike, K.; Kaneko, J.; Ohmoto, T. *Phytochemistry* **1994**, *37*, 579–584. For compound **2**, see: Grieco, P. A.; Vander Roest, J. M.; Pineiro-Nunez, M. M.; Campaigne, E. E.; Carmack, M. *Phytochemistry* **1995**, *38*, 1463–1465. For compound **3**, see: Itokawa, H.; Qin, X.-R.; Morita, H.; Takeya, K. *J. Nat. Prod.* **1993**, *56*, 1766–1771.

(4) For earlier publications in this series, see: Donahue, M. G.; Hart, D. J. *Can. J. Chem.* **2004**, *82*, 314–317. Hart, D. J.; Yang, D. *Heterocycles* **2007**, *73*, 197–201.

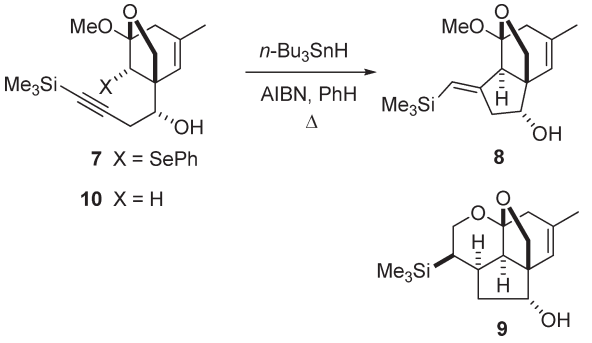
(5) For a preliminary account of work shown in Schemes 1 and 2, see: Cwynar, V.; Donahue, M. G.; Hart, D. J.; Yang, D. *Org. Lett.* **2006**, *8*, 4577–4580.

Published on Web 10/15/2009 DOI: 10.1021/jo901834q

SCHEME 1



SCHEME 2

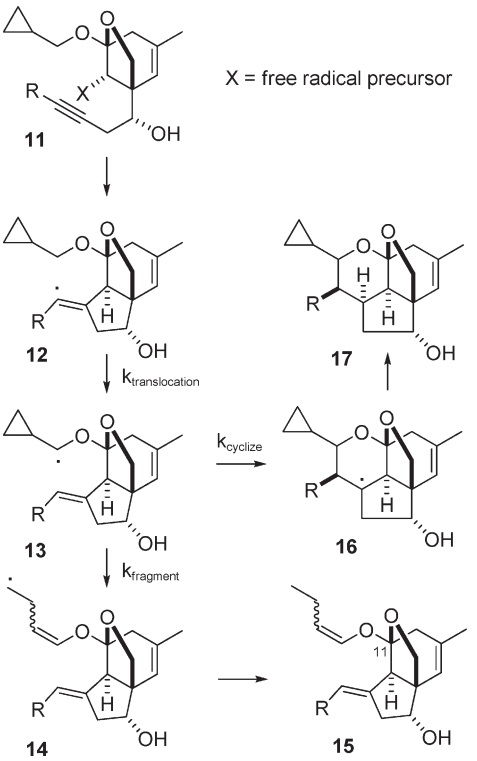


31% yield, along with 42% of the anticipated product **5** (Scheme 1).[6] A labeling experiment (*n*-Bu_3SnD) indicated that 93% of **5** incorporated a single deuterium in the C_{11} methoxy group. This suggested that increasing the concentration of tri-*n*-butyltin hydride would afford more **5** at the expense of **6** and indeed this was the case (Scheme 1). This was not an operationally pleasant solution to the problem, however, because the product had to be separated from large amounts of excess tin hydride and other tin-containing materials.[6]

Similar results were obtained with cyclization substrate **7** (Scheme 2). In this case the rate of cyclization of the initial radical generated from **7** was slower than the initial radical generated from bromide **4**. Therefore we were *never* able to obtain high yields of the desired cyclization product **8**. The major product was **10** (57% yield) at high tri-*n*-butyltin hydride concentrations and **9** (72%) at low concentrations of tri-*n*-butyltin hydride.[6]

The results shown in Schemes 1 and 2 posed the following problem. How could high yields of products of type **5** and **8** be obtained without intervention of the cyclization−atom transfer−cyclization (to give **6** and **9**) or reduction (to give **10**)? The first solution we investigated was based on the plan set forth in Scheme 3. We reasoned that a substrate of type **11** (R = $SiMe_3$ or CO_2Et) would undergo radical generation and cyclization at low tin hydride concentrations. Based on our experience with substrates **4** and **7**, it seemed reasonable

SCHEME 3



that this would be followed by rapid radical translocation from **12** to provide **13**. Based on ample literature precedence, it was expected that fragmentation of **13** to afford **15** (via homoallylic radical **14**) would be faster than cyclization to provide **17** (via radical **16**).[7] This plan was not only expected to deal with the aforementioned difficulties but was also expected to provide a vinyl ether at C_{11}, which we thought might have advantages later in the synthesis when the time came to reveal the C_{11} hemiacetal of the polyandranes.

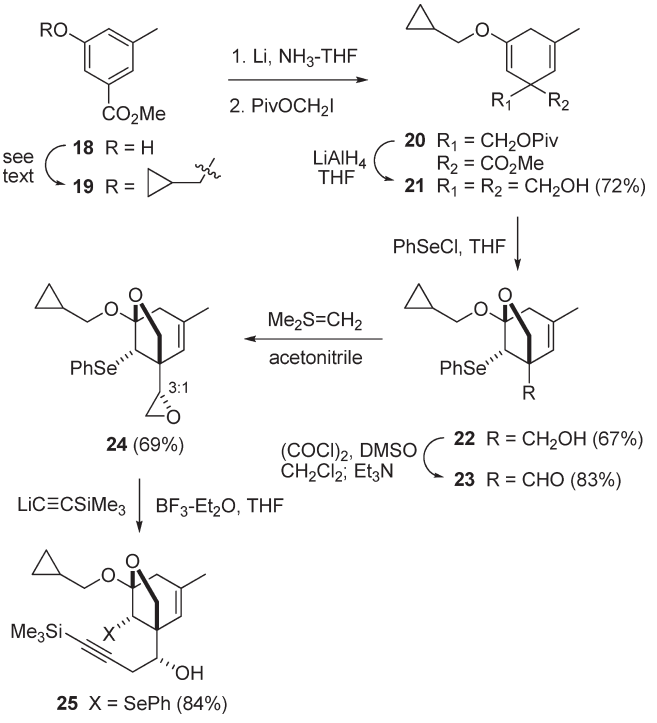
Results and Discussion

Our initial test of this plan began with a synthesis of cyclization substrate **25** (**11** where R = $SiMe_3$ and X = SePh). This represented a system for which adjusting tin hydride concentration had not provided a solution to the problem at hand (Scheme 2). The synthesis of this substrate is presented in Scheme 4. Treatment of phenol **18** with cyclopropylcarbinol under Mitsunobu conditions gave **19** in 82% yield.[8,9] Birch reductive alkylation of **19** using iodomethyl pivalate gave **20**, which was reduced to provide diol **21** in 72% overall yield.[10,11] Treatment of **21** with phenylselenenyl chloride provided **22** in 67% yield.[12] Swern oxidation of **22** gave **23** in 82% yield.[13] Treatment of aldehyde **23** with dimethylsulfonium methylide provided a separable 3:1 mixture of epoxide **24** and its C_7 diastereomer in a combined

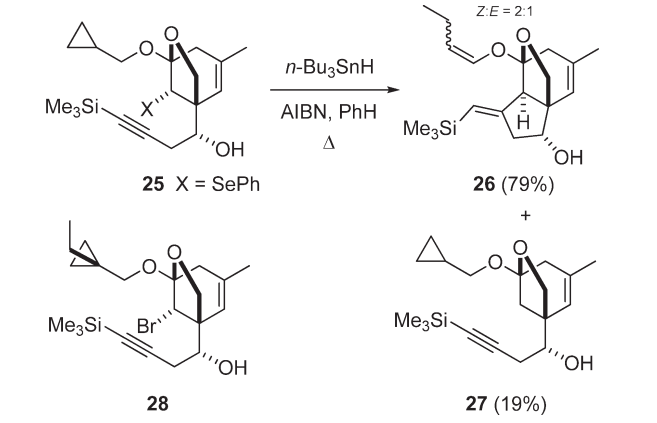
(6) Compounds **5** and **6** were obtained in 42% and 31% yields, respectively, when the initial concentrations of **4** and *n*-Bu_3SnH were 8.8 and 18 mM, respectively. Compounds **5** and **6** were obtained in 75% and 10% yields, respectively, when the initial concentrations of **4** and *n*-Bu_3SnH were 10 and 100 mM, respectively (see the Supporting Information for details of the cyclizations shown in Schemes 1 and 2).

(7) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317–323.
(8) Turner, F. A.; Gearien, J. E. *J. Org. Chem.* **1959**, *24*, 1952.
(9) Mitsunobu, O. *Synthesis* **1981**, 1–28.
(10) Van Bekkum, H.; Van Den Bosch, C.; Van Minnenpathuis, G.; DeMos, J. C.; van Wijk, A. M. *Recueil* **1971**, *90*, 137–149.
(11) Schultz, A. G.; Taylor, R. E. *J. Am. Chem. Soc.* **1992**, *114*, 3937.
(12) Nicolaou, K. C.; Lysenko, Z. *Tetrahedron Lett.* **1977**, 1257–1260.
(13) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

SCHEME 4



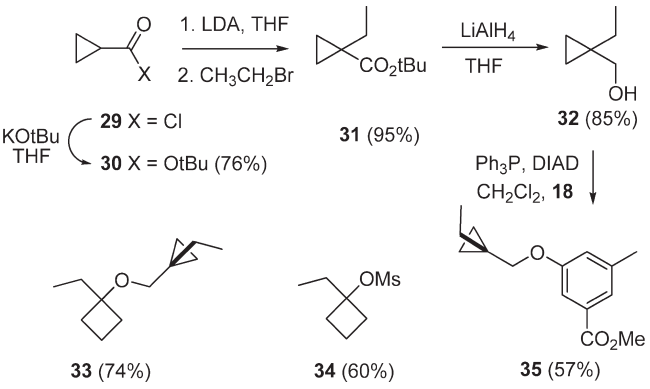
SCHEME 5



69% yield.[14] The stereochemical assignment at C_7 was inferred from similar compounds prepared during the course of this research (vide infra). Treatment of epoxide **24** with the organometallic reagent derived from lithium trimethylsilylacetylide and boron trifluoride etherate gave an 84% yield of **25**.[15]

The cyclization of **25** proceeded as expected, giving **26** as the major product (2:1 mixture of *Z* and *E* geometrical isomers, respectively) in 79% combined yield along with reduction product **27** in 19% yield (Scheme 5).[16] These results were regarded as a partial success. The operational problem of dealing with mixtures of vinyl ether geometrical isomers, however, led us to evaluate a modification of the plan shown in Scheme 3. We decided to introduce an ethyl group into the cyclopropane that would eliminate the possibility of geometrical isomerism. Thus, we set out to prepare cyclization substrate **28**.

SCHEME 6



The synthesis of the required reductive alkylation substrate was somewhat interesting (Scheme 6). We began by preparing *tert*-butyl cyclopropanecarboxylate (**30**) in 76% yield from the commercially available acid chloride **29**.[17] Alkylation of the lithium enolate derived from **30**, with bromoethane, gave **31** in 95% yield. Reduction of the ester provided cyclopropylcarbinol **32** in 85% yield. The next task was to alkylate phenol **18** with alcohol **32**. We began by trying to prepare the triflate of **32** (Tf_2O, pyridine, CH_2Cl_2), but instead obtained ether **33** (74%). An attempt to prepare the corresponding mesylate ($MeSO_2Cl$, pyridine, CH_2Cl_2) resulted in formation of rearranged mesylate **34** (60%). The coupling of **18** and **32** was eventually accomplished using a classical Mitsunobu reaction to give **35** in a 57% yield.[9]

With the reductive alkylation substrate **35** in hand, the synthesis of **28** followed established protocols (Scheme 7). Reductive alkylation of **35** was followed by lithium aluminum hydride reduction to provide diol **36** (55%). The diol was subjected to bromoetherification conditions to provide **37**.[18] A Swern oxidation gave **38** and sulfur ylide chemistry gave **39** as a 2:1 mixture of geometrical isomers (major isomer shown) that was separated by column chromatography.[14] Alcohol **37** and aldehyde **38** decomposed quickly, and this sequence had to be conducted without storing these intermediates as indicated in the Experimental Section. Epoxide **39** was opened with the appropriate acetylide to give a 90% yield of **28**.[15,19]

Free-radical cyclization of **28** gave the desired product **40** in 40% yield (Scheme 8). Another unanticipated reaction, however, reared its head. The other product of this reaction was **41** (42%), isolated as a 2:1 mixture of geometrical isomers. Thus, the initially formed radical apparently undergoes a 1,6-hydrogen atom transfer to give **42** at about the same rate as which it cyclizes. Fragmentation of **42** and reduction of the resulting radical provides **41**.

(14) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345–1353. Kutsuma, T.; Nagayama, I.; Okazaki, T.; Sakamoto, T.; Akaboshi, S. *Heterocycles* **1977**, *8*, 397.

(15) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394.

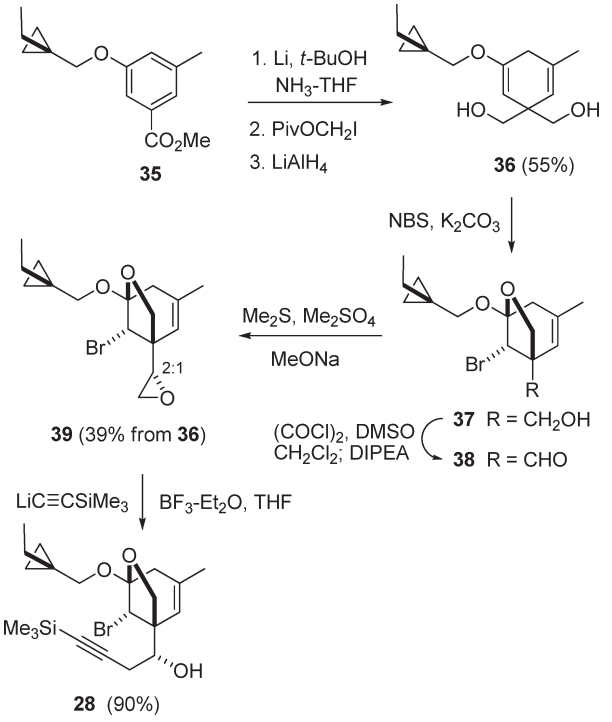
(16) Compounds **26** and **27** were characterized as a mixture. Manipulation of this mixture provided compounds **26** (free of **27**) as a mixture (see the Supporting Information for details).

(17) For some relevant literature, see: Gorrichon, L.; Maroni, P.; Zedde, C.; Dobrev, A. *J. Organomet. Chem.* **1983**, *252*, 267–274. Haener, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1655–65. Reichelt, I.; Reissig, H. U. *Chem. Ber.* **1983**, *116*, 3895–914.

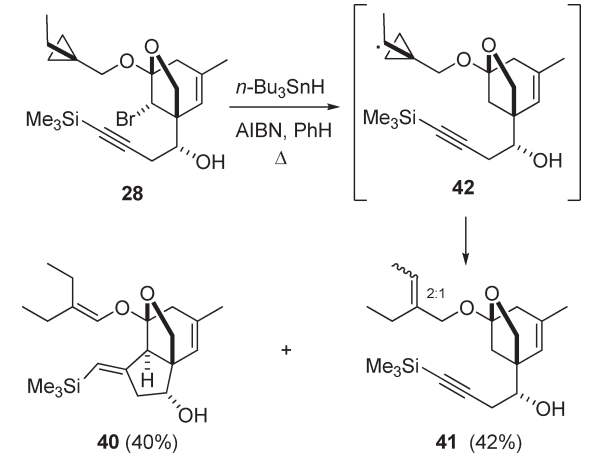
(18) Omission of the K_2CO_3 (acid sponge) resulted in formation of a large number of products.

(19) Alcohol **40** was sensitive and was used in the subsequent free-radical cyclization on the same day it was prepared.

SCHEME 7



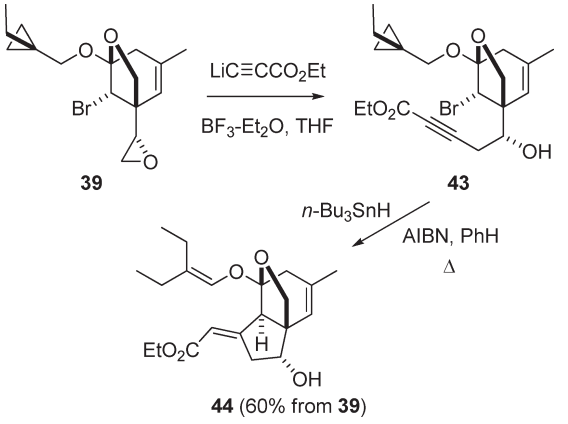
SCHEME 8



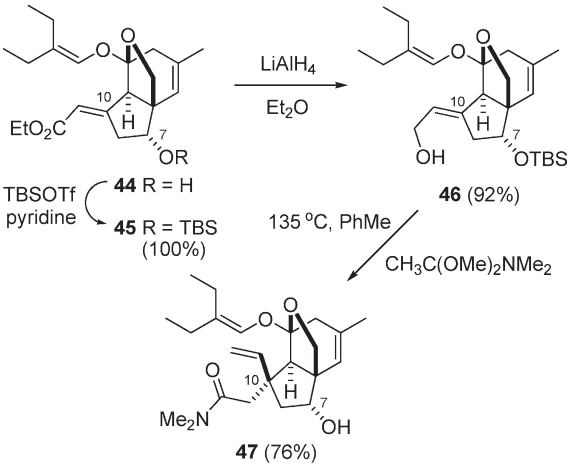
This unwanted diversion led us to examine **43**, prepared from **39** as shown in Scheme 9. We knew that this electron-deficient acetylene would be a better radical acceptor than silyl acetylene **28** and anticipated that cyclization would compete favorably with the aforementioned 1,6-H-atom transfer. This proved to be the case as perhydroindan **44** was obtained in 60% overall yield from **39**.

At this point, we had developed syntheses of at least two compounds (**26** and **44**) that held some promise as intermediates in projected approaches to the polyandranes. From compound **44**, we hoped that the endocyclic olefin and C_7 hydroxyl group would provide handles for introduction of the required C- and D-ring functionality. We also hoped the unsaturated ester might serve as a handle for introduction of the C_{10} furanone. One promising reaction sequence directed toward the latter goal is shown in Scheme 10. Protection of

SCHEME 9



SCHEME 10



the C_7 hydroxyl group provided TBS ether **45**.[20] Reduction of the ester with lithium aluminum hydride gave alcohol **46** in 92% overall yield from **44**. An Eschenmoser−Claisen rearrangement converted **46** to amide **47** in 76% yield with good control of stereochemistry at C_{10}.[21] An unattractive feature of this approach, however, is that it will require degradation of a vinyl group to a methyl group at C_{10}.

We also thought that vinylsilane **26** might be a useful intermediate. For example, we were able to convert **26** into cyclopentenone **48** using a two-step oxidation−isomerization/desilylation sequence (Scheme 11).[22,23] This intermediate is attractive because it might provide a handle for establishing the C_{10} quaternary carbon, with the desired methyl group in place, via conjugate addition chemistry. A drawback to this approach, however, is that alcohol stereochemistry at C_7 would have to be reestablished at a later stage of the synthesis.

The unsatisfactory aspects of **26** and **44** as possible intermediates in a total synthesis led us to explore another

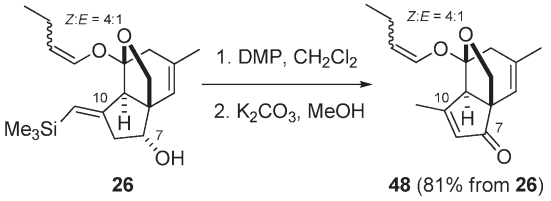
(20) Stewart, Ray F.; Miller, Larry L. *J. Am. Chem. Soc.* **1980**, *102*, 4999–5004. Corey, E. J.; Cho, H.; Ruecker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455–3458.

(21) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425–2429.

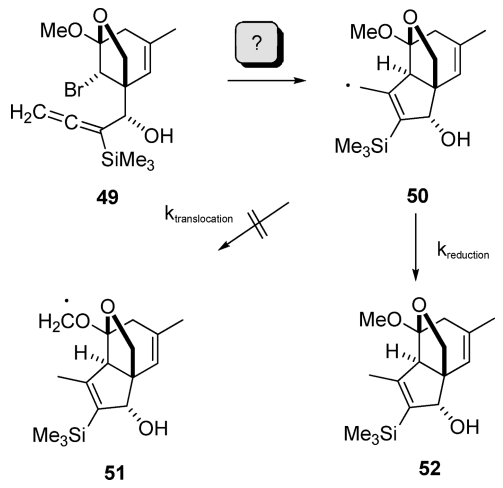
(22) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(23) For an analogous isomerization−desilylation, see: Paquette, L. A.; Wells, G. J.; Horn, K. A.; Yan, T.-H. *Tetrahedron Lett.* **1982**, *23*, 263–266.

SCHEME 11



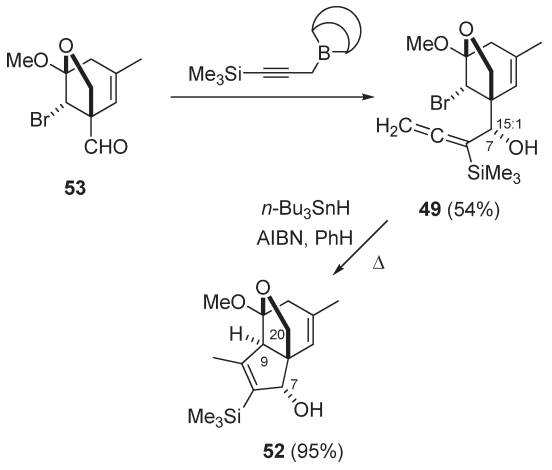
SCHEME 12



solution to the radical translocation problems described in Schemes 1 and 2. The idea is described in Scheme 12. We imagined that an allenic cyclization substrate such as **49** would provide allylic radical **50**.[24,25] Radical **50** is no longer geometrically disposed to undergo a 1,6-hydrogen atom transfer to provide **51**, and we thought it would probably simply be reduced to give perhydroindan **52**. If this was the case, one can imagine ways to use the cyclopentenol substructure of **52** to introduce the C_{10} furanone. Even if radical translocation were to occur, it seemed unlikely that **51** would undergo a cyclization at an appreciable rate. The product of such a cyclization would be a strained *trans*-fused oxabicyclo[3.3.0]octane![26]

Cyclization substrate **49** was prepared from aldehyde **53** by reaction with the borane derived from lithiated 1-trimethylsilylpropyne and 9-methoxy-9-BBN in the presence of boron trifluoride etherate (Scheme 13).[27] This reaction provided **49** in 51% yield along with 3% of the corresponding C_7-diastereomer. This reaction not only gave the desired cyclization substrate but also provided a solution

SCHEME 13



to controlling stereochemistry at C_7 without the need for chromatographic separation. Treatment of **49** with tri-*n*-butyltin hydride gave the expected cyclization product **52** in 95% yield. Evidence supporting the assigned stereochemistry at C_7 and C_9 was obtained by a series of NOE experiments that revealed the proximity of the C_7 and C_{20} hydrogens and an absence of an interaction between the C_7 and C_9 hydrogens. A more direct proof of stereochemistry was obtained by X-ray crystallography of the cyclization product derived from the C_7 isomer of **49**.[28]

Conclusions

In summary, this paper describes two solutions to problems encountered during the course of attempts to develop a free-radical cyclization strategy for the synthesis of the polyandranes. Although we would have preferred to foresee the problems that were encountered (Schemes 1, 2, and 8), this research demonstrates that logical solutions to these problems could be developed. Although this will not always be the case, we hope that our observations are helpful to others as they develop their own radical cyclization strategies to molecules of interest.

Experimental Section

3-(1-Ethylcyclopropyl)methoxy-5-methyl-2,5-cyclohexadiene-1,1-dimethanol (36). To a solution of 5.0 g (20.2 mmol) of ester **35** and 1.55 g (21.0 mmol) of *tert*-butyl alcohol in 50 mL of dry THF at −78 °C under N_2 was added 90 mL of liquid ammonia. To the mixture was added 0.32 g (46.2 mmol) of lithium in small pieces over a period of 30 min. The resulting dark blue solution was stirred for 30 min, and the excess lithium was then destroyed by addition of 0.1 mL of 1,3-pentadiene. To the resulting pale yellow solution was added a solution of 4.91 g (20.2 mmol) of freshly prepared iodomethyl pivalate[29] in 20 mL of dry THF via an addition funnel. The mixture was stirred for 2 h, and the reaction was then quenched by addition of 2.4 g (45.3 mmol) of solid NH_4Cl. The ammonia was allowed to evaporate over 2 h

(24) For radical cyclizations in which allenes are the acceptor, see: Apparu, M.; Crandall, J. K. *J. Org. Chem.* **1984**, *49*, 2125–2130. Hart, D. J. *Science* **1984**, *223*, 883–887. Dener, J. M.; Hart, D. J. *Tetrahedron* **1988**, *44*, 7037–7046. For other relevant cyclizations, see: Roumestant, M. L.; Arseniyadis, S.; Gore, J.; Laurent, A. *J. Chem. Soc., Chem. Commun.* **1976**, 479–480. Pattenden, G.; Robertson, G. M. *Tetrahedron Lett.* **1983**, *24*, 4617–4620.

(25) It is also possible that the slow rate at which allylic radicals undergo hydrogen atom transfer may also contribute to the success of this strategy. For some relevant references, see: Hayes, C. J.; Burgess, D. R. Jr. *J. Phys. Chem. A* **2009**, *113*, 2473–2482. DeZutter, C. B.; Horner, J. H.; Newcomb, M. *J. Phys. Chem. A* **2008**, *112*, 1891–1896. Stork, G.; Reynolds, M. E. *J. Am. Chem. Soc.* **1988**, *110*, 6911–6913.

(26) For strain in bicyclo[3.3.0]octanes, see: Barrett, J. W.; Linstead, R. P. *J. Chem. Soc.* **1935**, 436–442.

(27) Wang, K. K.; Liu, C. *J. Org. Chem.* **1985**, *50*, 2578–2580.

(28) Tri-*n*-butyltin hydride mediated cyclization of 7-*epi*-**49** provided 7-*epi*-**52** (mp 101−105 °C) in 63% yield. The structure of this compound was established by X-ray crystallography.

(29) Prepared from commercially available chloromethyl pivalate using a Finkelstein reaction (36 mmol of chloromethyl pivalate and 54 mmol of sodium iodide in 40 mL of acetone at room temperature for 12 h) and used within 24 h: Finkelstein, H. *Chem. Ber.* **1910**, *43*, 1528–1532.

under N_2. The mixture was filtered and concentrated in vacuo to give 7.31 g of a pale yellow oil which showed one spot by TLC (silica gel, hexanes−ethyl acetate, 2:1). The pale yellow oil was used directly in the next reaction without further purification. To a slurry of 1.6 g (42.0 mmol) of lithium aluminum hydride in 50 mL of diethyl ether cooled to −78 °C (dry ice−acetone bath) was added a solution of 7.31 g (20.1 mmol) of the crude diester in 20 mL of diethyl ether over 20 min. The mixture was allowed to stir at −78 °C for 5 h and then at room temperature for 16 h. The mixture was cooled in an ice−water bath and quenched by slow sequential addition of 1.6 mL of water, 1.6 mL of 15% aqueous sodium hydroxide, and 4.8 mL of water over 2 h. The mixture was stirred for another 6 h and filtered, and the filter cake was rinsed with two 20-mL portions of diethyl ether. The filtrate was dried ($MgSO_4$), filtered, and concentrated in vacuo to give a mixture of white solid and yellow oil from which 3.03 g (60%) of diol **36** was separated via filtration as a white solid: mp 105−107 °C; IR (in $CHCl_3$) 3312, 2870, 1694, 1658 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 0.42 (m, 2H, CH_2), 0.47 (m, 2H, CH_2), 0.96 (t, J = 7.5 Hz, 3H, CH_3), 1.48 (q, J = 7.5 Hz, 2H, CH_2), 1.64 (t, J = 6.0 Hz, 2H, OH), 1.82 (s, 3H, CH_3), 2.71 (s, 2H, =CCH_2), 3.47 (m, 4H, CH_2OH), 3.58 (s, 2H, OCH_2), 4.41 (s, 1H, OC=CH), 5.29 (s, 1H, C=CH); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 9.7 (t), 10.44 (q), 20.4 (s), 22.5 (q), 27.3 (t), 34.1 (t), 47.6 (s), 68.8 (t), 71.9 (t), 93.1 (d), 121.9 (d), 134.6 (s), 156.4 (s); exact mass calcd for $C_{15}H_{24}O_3$ (M + Na)$^+$ m/z 275.1623, found m/z 275.1630. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.15; H, 9.80.

***rel*-(1*R*,5*S*,8*S*)-8-Bromo-5-(1-ethylcyclopropyl)methoxy-3-methyl-6-oxabicyclo[3.2.1]oct-2-ene-1-methanol (37).** To a solution of 1.5 g (6.0 mmol) of diol **36** in 22 mL of dry dichloromethane at 0 °C (dry ice−acetone) was added 1.0 g (7.2 mmol) of powdered potassium carbonate, followed by slow addition of 1.24 g (6.3 mmol) of solid *N*-bromosuccinimide over 5 min. The solution was stirred for 5 min and then poured into 20 mL of water. The aqueous phase was extracted with two 20-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a solution of the alcohol **37** in 10 mL of dichloromethane which was used immediately in the next step. Due to instability of pure alcohol in air or even when stored in solvents, only ^1H NMR spectral data were collected: ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.39 (m, 2H, CH_2), 0.43 (m, 2H, CH_2), 0.96 (t, J = 7.2 Hz, 3H, CH_3), 1.44 (q, J = 7.2 Hz, 2H, CH_2), 1.75 (s, 3H, =CCH_3), 2.32 and 2.68 (ABq, J = 17.2 Hz, 2H, CH_2C=), 2.42 (m, 1H, OH), 3.37, 3.53 (ABq, J = 9.6 Hz, 2H, CH_2O), 3.68 (m, 2H, CH_2OH), 3.86, 4.08 (ABq, J = 6.8 Hz, 2H, CH_2O), 4.47 (s, 1H, CHBr), 5.22 (s, 1H, =CH). An impurity (probably succinimide) appeared as a singlet at δ 2.8 in the ^1H NMR spectrum.

***rel*-(1*S*,5*S*,8*S*)-8-Bromo-5-(1-ethylcyclopropyl)methoxy-3-methyl-6-oxabicyclo[3.2.1]oct-2-ene-1-carboxaldehyde (38).** To a solution of 1.22 g (9.6 mmol, 0.82 mL) of oxalyl chloride in 30 mL of dry dichloromethane at −78 °C (dry ice−acetone) was added a solution of 1.5 g (19.2 mmol, 1.36 mL) of dry dimethyl sulfoxide by syringe over 2 min. The solution was stirred cold for 30 min, and a solution of 1.98 g (6.0 mmol) of alcohol **37** (material from previous reaction) in 10 mL of dry dichloromethane was added by cannula over 10 min. The solution was stirred cold for 2 h, and 3.9 g (30 mmol, 5.0 mL) of diisopropylethylamine was added via a syringe. The mixture was stirred cold for 30 min and then warmed to room temperature. The mixture was poured into 50 mL of dichloromethane in an ice bath and then washed with three 50-mL portions of 4% aqueous NH_4Cl and 10 mL of saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 1.97 g of aldehyde **38** as a brown oil that was sufficiently pure for the next reaction: IR 3072, 2730, 1730 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.41 (m, 2H, CH_2), 0.55 (m, 2H, CH_2), 1.11 (t, J = 7.6 Hz, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.59 (q, J = 7.6 Hz, 2H, CH_2), 2.42 and 2.81 (ABq, J = 17.6 Hz, 2H, CH_2C=), 3.36 and 3.53 (ABq, J = 8.8 Hz, 2H, CH_2O), 3.62 and 3.76 (ABq, J = 5.8 Hz, 2H, CH_2O), 4.50 (s, 1H, CHBr), 5.77 (s, 1H, =CH), 9.18 (s, 1H, CHO); ^{13}C NMR (C_6D_6, 100 MHz) δ 10.1 (t), 10.3 (t), 10.8 (q), 20.7 (s), 21.5 (q), 27.3 (t), 43.1 (t), 47.7 (d), 59.4 (s), 66.9 (t), 73.7 (t), 107.2 (s), 118.4 (d), 136.9 (s), 197.0 (d); exact mass calcd for $C_{15}H_{21}{}^{79}BrO_3$ (M + Na)$^+$ m/z 351.0572, found m/z 351.0579. This material exhibited signals due to impurities in the NMR spectra (see the Supporting Information).

(1*S*,5*S*,8*S*)-*rel*-8-Bromo-5-(1-ethylcyclopropyl)methoxy-3-methyl-1-[(2*S*)-2-oxiranyl]-6-oxabicyclo[3.2.1]oct-2-ene (39) and (1*S*,5*S*,8*S*)-*rel*-8-Bromo-5-(1-ethylcyclopropyl)methoxy-3-methyl-1-[(2*R*)-2-oxiranyl]-6-oxabicyclo[3.2.1]oct-2-ene (7-*epi*-39). To a solution of 1.14 g (9.0 mmol) of dimethyl sulfate in 3 mL of acetonitrile was added a solution of 0.62 g (9.9 mmol) of dimethyl sulfide in 2 mL of acetonitrile. After being stirred at room temperature overnight, the mixture was cooled in an ice bath, and 0.54 g (9.9 mmol) of sodium methoxide was added. After 30 min, the mixture became a milky suspension. A solution of 1.97 g (6.0 mmol) of aldehyde **38** in 5 mL of acetonitrile was added dropwise. After being stirred for 30 min, the reaction gradually turned dark green. The suspension was concentrated in vacuo, and the residue was washed with 10 mL of water. The aqueous phase was extracted with two 10-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (hexanes−ethyl acetate, 5:1) to afford 1.28 g of a 2:1 mixture of diastereomeric epoxides **39** and 7-*epi*-**39** as a colorless oil. This material contained starting aldehyde as an impurity. The oil was chromatographed again using MPLC (hexanes−ethyl acetate, 20:1) to afford 0.53 g (26%) of epoxide **39** and 0.26 g (13%) of 7-*epi*-**39** as colorless oils. Epoxide **39**: IR 3072, 2875, 1665 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.27 (m, 2H, CH_2), 0.42 (m, 2H, CH_2), 0.99 (t, J = 7.5 Hz, 3H, CH_3), 1.44 (s, 3H, =CCH_3), 1.48 (m, 2H, C$H_2$$CH_3$), 2.12 and 2.27 (m, 2H, oxirane-CH_2), 2.34 and 2.77 (ABq, J = 18.0 Hz, 2H, CH_2C=), 2.67 (m, 1H, oxirane-CH), 3.25 and 3.45 (ABq, J = 9.0 Hz, 2H, CH_2O), 3.61 and 3.66 (ABq, J = 7.0 Hz, 2H, CH_2O), 4.45 (s, 1H, CHBr), 5.15 (s, 1H, =CH); ^{13}C NMR (C_6D_6, 125 MHz) δ 10.0 (t), 10.2 (t), 10.7 (q), 20.6 (s), 21.5 (q), 27.3 (t), 42.8 (t), 42.9 (t), 48.2 (s), 50.7 (d), 51.0 (d), 66.4 (t), 74.7 (t), 106.8 (s), 119.7 (d), 136.3 (s); exact mass calcd for $C_{16}H_{23}{}^{79}BrO_3$ (M + Na)$^+$ m/z 365.0728, found m/z 365.0723. Epoxide 7-*epi*-**39**: IR (neat) 3073, 2875, 1664 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.33 (m, 2H, CH_2), 0.47 (m, 2H, CH_2), 1.02 (t, J = 7.2 Hz, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.51 (q, J = 7.2 Hz, 2H, C$H_2$$CH_3$), 2.23 and 2.66 (m, 2H, oxirane-CH_2), 2.38 and 2.81 (ABq, J = 17.6 Hz, 2H, CH_2C=), 2.59 (m, 1H, oxirane-CH), 3.30 and 3.49 (ABq, J = 8.8 Hz, 2H, CH_2O), 3.72 (s, 2H, CH_2O), 4.26 (s, 1H, CHBr), 5.19 (s, 1H, =CH); ^{13}C NMR (C_6D_6, 125 MHz) δ 10.0 (t), 10.2 (t), 10.7 (q), 20.6 (s), 21.4 (q), 27.3 (t), 43.1 (t), 43.2 (t), 47.7 (s), 49.6 (d), 51.8 (d), 66.5 (t), 75.3 (t), 107.1 (s), 121.8 (d), 135.8 (s); exact mass calcd for $C_{16}H_{23}{}^{79}BrO_3$ (M + Na)$^+$ m/z 365.0728, found m/z 365.0723. This material contained trace impurities by NMR.

Ethyl (5*R*)-*rel*-5-[(1*S*,5*S*,8*S*)-8-Bromo-5-(1-ethylcyclopropyl)-methoxy-3-methyl-6-oxabicyclo[3.2.1]oct-2-en-1-yl]-2-pentynoate (43). To a solution of 1.1 g (11.2 mmol, 1.14 mL) of ethyl propiolate in 20 mL of freshly distilled THF, cooled to −85 °C (ethyl acetate−liquid nitrogen), was added 4.48 mL (11.2 mmol) of 2.5 M *n*-butyllithium in hexanes, and the mixture was stirred for 10 min. To the solution was added 1.5 mL (1.6 g, 11.2 mmol) of boron trifluoride etherate via a syringe followed by stirring for 5 min. A solution of 960 mg (2.8 mmol) of epoxide **39** in 5 mL of dry tetrahydrofuran was then added via a syringe, followed by 1 mL of tetrahydrofuran rinse. The mixture was stirred for 3 h at −85 °C. The temperature was warmed to room temperature,

and then 5 mL of saturated aqueous $NaHCO_3$ was added to quench the reaction. The aqueous phase was extracted with two 20-mL portions of ether. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a colorless oil. The oil was immediately chromatographed over 30 g of silica gel (hexanes−ethyl acetate, 10:1), and the resulting **43** was concentrated as a solution in 20 mL of degassed benzene and immediately used in the next step. Due to instability of pure alcohol in air, only NMR spectral data were collected: ^{1}H NMR (C_6D_6, 500 MHz) δ 0.25 (m, 2H, CH_2), 0.42 (m, 2H, CH_2), 0.89 (t, J = 7.0 Hz, 3H, CH_3), 0.99 (t, J = 7.5 Hz, 3H, CH_3), 1.45 (s, 3H, =CCH_3), 1.48 (m, 2H, C$H_2$$CH_3$), 1.76 (dd, J = 17.0, 9.0 Hz, 1H, CH_2CHOH), 1.83 (d, J = 5.0 Hz, 1H, OH), 2.10 (dd, J = 17.0, 2.5 Hz, 1H, CH_2CHOH), 2.37 and 2.77 (ABq, J = 17.5 Hz, 2H, =CCH_2), 3.33 and 3.52 (ABq, J = 9.0 Hz, 2H, OCH_2), 3.52 (m, 1H, C*H*OH), 3.61 and 3.96 (ABq, J = 6.5 Hz, 2H, OCH_2), 3.92 (q, J = 7.0 Hz, 2H, OC$H_2$$CH_3$), 4.63 (s, 1H, CHBr), 4.84 (s, 1H, =CH); ^{13}C NMR (C_6D_6, 125 MHz) δ 10.0 (t), 10.2 (t), 10.7 (q), 13.6 (q), 20.6 (s), 21.6 (q), 22.8 (t), 27.3 (t), 43.2 (t), 50.3 (d), 51.8 (s), 61.4 (t), 66.4 (t), 68.4 (d), 72.7 (t), 75.5 (s), 85.4 (s), 106.5 (s), 121.1 (d), 136.6 (s), 153.2 (s).

***rel*-(1*E*,3*R*,3a*S*,7*R*,7a*R*)-7-(2-Ethyl-1-butenyloxy)-1,2,3,6,7,7a-hexahydro-1,5-dimethyl-1-[(carbethoxy)methylene]-7,3a-(epoxymethano)-3a*H*-inden-3-ol (44).** To a solution of 1.23 g (2.8 mmol) of **43** in 130 mL of dry, degassed benzene at 105 °C was added 1.22 g (4.2 mmol) of tri-*n*-butylstannane and 115 mg (0.70 mmol) of azo-bis-isobutyronitrile in 10 mL of dry, degassed benzene over a period of 1 h. The mixture was warmed under reflux for 1 h and then concentrated in vacuo. The residual crude oil was purified by chromatography over 30 g of silica gel (hexanes−ethyl acetate, 5:1) to afford 608 mg (60% from epoxide **39**) of **44** as a colorless oil: IR (neat) 3477, 2966, 1713, 1658 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 0.94 (t, J = 7.5 Hz, 3H, CH_3), 0.98 (t, J = 7.0 Hz, 3H, CH_3), 1.02 (m, 1H, OH), 1.18 (t, J = 7.5 Hz, 3H, CH_3), 1.42 (s, 3H, =CCH_3), 1.91 (q, J = 7.5 Hz, 2H, C$H_2$$CH_3$), 2.31 (m, 2H, C$H_2$$CH_3$), 2.31 and 2.58 (ABq, J = 17.0 Hz, 2H, =CCH_2), 3.04 (s, 1H, CH), 3.08 (dd, J = 20.5, 2.5 Hz, 1H, CH_2CHOH), 3.57 (m, 1H, CH_2CHOH), 3.37 and 3.54 (ABq, J = 7.5 Hz, 2H, OCH_2), 3.56 (m, 1H, C*H*OH), 4.05 (q, J = 7.5 Hz, 2H, OC$H_2$$CH_3$), 5.62 (s, 1H, =CH), 6.49 (s, 1H, =CHOR), 6.88 (m, 1H, =C*H*CO_2Et); ^{13}C NMR (C_6D_6, 125 MHz) δ 12.7 (q), 13.0 (q), 14.0 (q), 20.6 (t), 21.5 (q), 24.7 (t), 43.5 (t), 47.0 (t), 55.9 (d), 58.4 (s), 59.3 (t), 70.4 (d), 77.4 (t), 110.4 (s), 117.8 (d), 124.1 (s), 126.3 (d), 133.1 (d), 134.7 (s), 158.4 (s), 166.3 (s); exact mass calcd for $C_{21}H_{30}O_5$ $(M + Na)^+$ m/z 385.1991, found m/z 385.1990.

Supporting Information Available: Experimental procedures and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.