JOC Article

Synthesis and Structure of Hydroxyl Acids of General Structure 7,7-Alkenyl/alkynyl-5-hydroxymethyl-6-oxabicyclo[3.2.1]octane-1-carboxylic Acid

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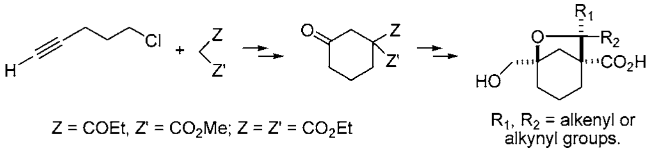

The open-ended hollow tubular structure formed by inclusion of water molecules in the packing of the hydroxyl acid **1** ($R_1 = CH_2OH$, R_2 = ethyl groups) led to the synthesis and structural study of their unsaturated analogues. In this article we report on a general and practical large-scale synthesis of hydroxyl acids that possess alkenyl and alkynyl appendages. Substitution of the ethyl groups in **1** with unsaturated two-carbon appendages has a different effect on the molecular structure and on the hydrogen-bonding pattern. No variation has been induced by substitution of only one ethyl group with a vinyl one, although the substitution of both ethyl groups with vinyl or acetylene appendages has the greatest effect on the molecular structure and results in different hydrogen-bonding motifs.

Introduction

An amphiphilic molecule would be found at the water/nonpolar solvent interface forming ordered, anhydrous or hydrated, H-bonding arrangements.[1,2] In principle, all aggregation options can be present in the equilibrium. However, at any given moment the nucleation of one of the aggregates progresses irreversibly toward a three-dimensional crystalline packing.[3] In solution, energy barriers between the different aggregations are low or nonexistent and conversion from one to the other in either direction is possible. At the moment of nucleation the energy barrier grows, equilibrium is interrupted, and the process continues irreversibly toward the building of the chosen crystalline structure. The anhydrous/hydrated molecular aggregate which crystallizes is the result of interconversions that take place in solution, associating molecular structural factors with the thermodynamic and kinetic principles ruling the equilibrium.[4,5] Thus, to the extent to which hydrated arrangements increase their H-bonding (ΔH decrease), their motions will decrease (ΔS decrease) and their relative intermolecular distances are shortened (ΔV decrease). The reverse also happens. This means that hydration/dehydration is the cause/effect of the

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§ Instituto de Química-Física Rocasolano.

(1) Recent studies of the ordering of amphiphilic molecules at liquid−liquid interfaces: (a) Steel, W. H.; Warker, R. A. *Nature* **2003**, 296−299. (b) Tikhonov, A. N.; Schlossman, M. L. *J. Phys. Chem. B* **2003**, *107*, 3344−3347. (c) Zhang, Z.; Mitrinovic, D. M.; Williams, S. M.; Huang, Z.; Schlossman, M. L. *J. Chem. Phys.* **1999**, *110*, 7421−7423.

(2) Revision articles: (a) Pratt, L. R.; Pohorille, A. *Chem. Rev.* **2002**, *102*, 2671−2692. (b) Richmond, G. L. *Chem. Rev.* **2002**, *102*, 2693−2724. (c) Kuzmenko, I.; Rapaport, A.; Kjaer, K.; Als-Nielsen, J.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Chem. Rev.* **2002**, *102*, 1659−1696.

(3) The central problem of nucleation, at the experimental and theoretical levels, is the determination of the rate of nucleation as a function of the controlling parameters: (a) Yau, S.-T.; Vekilov, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1080−1089. (b) Chin, D. N.; Palmore, G. T. R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 1, 2115−2122. (c) Talenquer, V.; Oxtoby, D. W. *J. Chem. Phys.* **1998**, *109*, 223−227. (d) Oxtoby, D. W. *Acc. Chem. Res.* **1998**, *31*, 91−97.

(4) (a) Williams, D. H.; O'Brien, D. P.; Bardsley, B. *J. Am. Chem. Soc.* **2001**, *123*, 737−738. (b) Searly, M. S.; Williams, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 10690−10697.

(5) The hydration cost is more dependent on the number of water H bonds than on their strength. Hence, the closer water is to an aqueous/nonpolar solvent interface transition, the stronger the expected hydrophobic assembly. For an experimental study that probes the weakness of water H-bonding at H_2O/CCl_4 and H_2O/hydrocarbon interfaces, see: Scatena, L. F.; Brown, M. G.; Richmond, G. L. *Science* **2001**, *292*, 908−912.

10.1021/jo052237p CCC: $33.50

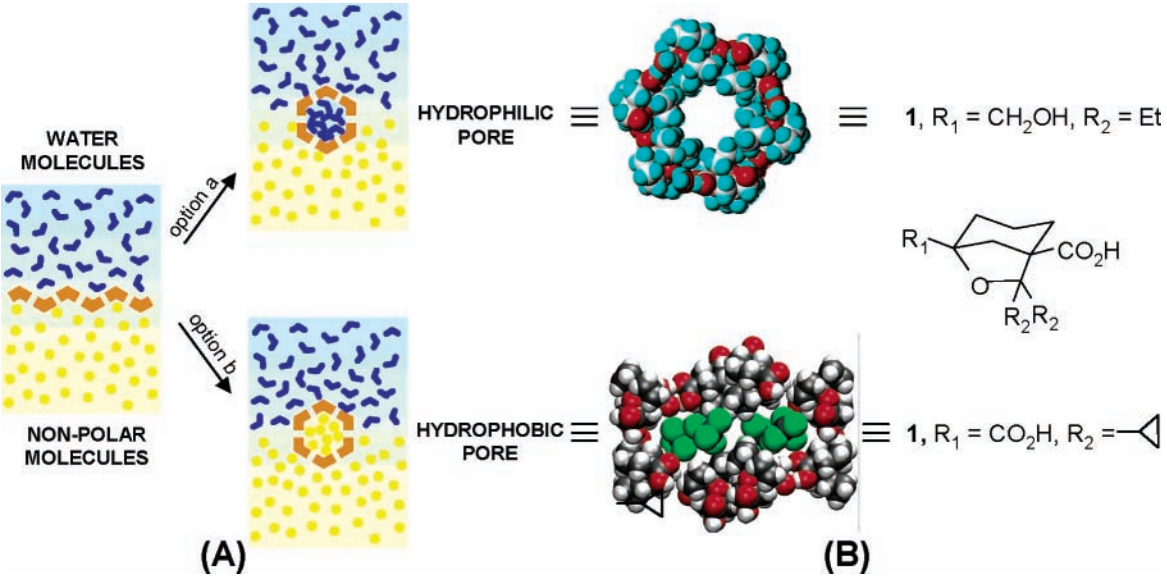

FIGURE 1. (A) Schematic drawing for chain-folding at the water/nonpolar solvent interface of an amphiphilic molecule forming, in competence, a hydrophilic pore or a hydrophobic pore. (B) Crystal structures obtained by crystallization at the water/carbon tetrachloride interface of hydroxy-acid **1** ($R_1 = CH_2OH$, $R_2 = Et$) (ref 8) and diacid **1** ($R_1 = CO_2H$, R_2 = cyclopropyl) (ref 12). In the first case, the pore is refilled by water molecules (hydrophilic). In the second case, the pore is refilled by carbon tetrachloride molecules (hydrophobic).

functional characteristics and structural specificities of each molecule.[6]

Research into the solid state of different homologues of the family of hydroxyl acids[7] of general structure **1** ($R_1 = CH_2OH$, R_2 = alkyl)[8] shows that all nucleation options are possible and that there is a single member of the family **1** ($R_1 = CH_2OH$, R_2 = ethyl) which is able to form, at the H_2O/CCl_4 interface, a cyclic two-dimensional organization which extends in the third dimension to form channels in the solid state (Figure 1). The result is that **1** ($R_1 = CH_2OH$, R_2 = ethyl) is the only one observed which optimizes, among all possible options, the packing to a channel-forming structure, where water molecules are incorporated in the structure and inner surface of the pore.[9]

The study in solid state of different members of the diacid[10] family **1** ($R_1 = CO_2H$, R_2 = alkyl)[11] shows that by slow crystallization from the H_2O/CCl_4 interface, the homologue **1** ($R_1 = CO_2H$, R_2 = cyclopropyl) contains the appendix of maximum volume allowed to give a hydrated structure in the crystalline state. For this particular molecule, crystallization at the H_2O/CCl_4 interface in an atmosphere of methane or ethane showed that the displacement of water takes place with chain folding and the creation of hydrophobic pores that are refilled, in competition with water, by nonpolar molecules[12] (Figure 1). The model illustrates how the assembly of hydrophobic moieties is enhanced by removal of water molecules from regions between these groups.[13]

Background

The retrosynthetic analysis identified as route A in Scheme 1 has proven to be highly efficient in the synthesis of hydroxyl acids of general structure **1a** when R and R′ are alkyl appendages. Thus, a large family of homologues of this general structure has been prepared, and the crystal packing of each of them has been studied in solid state.[8] Each homologue was synthesized using the carboxylic acid **5a** as a common precursor to all of them. Thus, following route A in the synthetic sense, dialkyl compounds were synthesized by condensing the dilithium salt of 3-methylenecyclohexanecarboxylic acid with the appropriate dialkyl ketone to give the hydroxyl acid **4a**, which was iodinated to the iodolactone **3a**. Base treatment of **3a** produced the unstable epoxide **2a**. The construction of the desired oxolane ring was stereoselectively carried out by treating crude epoxy alcohol **2a** with TMSOTf or TIPSOTf and 2,6-lutidine in CH_3NO_2 at 0 °C for 10−15 min. Brønsted acid-catalyzed cyclizations afforded mixtures of 6-endo-tet and 5-exo-tet compounds in some of the substrates studied.[14] However, for most of the epoxy alcohols studied with structure **2a**,

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(6) Revisions of general interest in the prediction and synthesis of crystalline aggregates: (a) Gavezotti, A. *Synlett* **2002**, 201−214. (b) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48−76. (c) Allen, F. H.; Motherwell, W. D. S.; Raithby, P. R.; Shields, G.; Taylor, R. *New J. Chem.* **1995**, 25−34. (d) Desiraju, G. R. *Angew. Chem., Int. Ed.* **1995**, *34*, 2311−2327. (e) Desiraju, G. R. *Crystal Engineering. The Design of Organic Solids*; Elsevier: Amsterdam, The Netherlands, 1985.

(7) A revision of related models of bile acids, the most studied hydroxyl-carboxylic acids ordering in the solid state: Miyata, M.; Sada, K. In *Comprehensive Supramolecular Chemistry*; McNicol, D. D., Toda, F., Bishop, R., Eds.; Pergamon: Oxford, 1996; Vol. 6, pp 147−175.

(8) (a) Carrasco, H.; Foces-Foces, C.; Pérez, C.; Rodríguez, M. L.; Martín, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 11970−11981. (b) Pérez, C.; Espínola, C. G.; Foces-Foces, C.; Núnez-Coello, P.; Carrasco, H.; Martín, J. D. *Org. Lett.* **2000**, *2*, 1185−1188.

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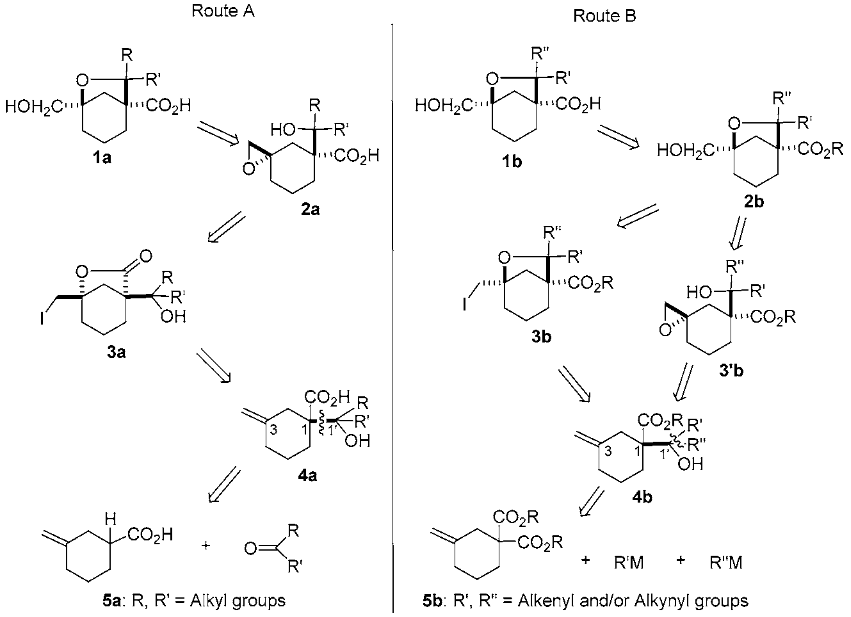
(10) Representative examples of dicarboxylic acid packing in solid state are: (a) Moorthy, J. N.; Natarajan, R.; Mal, P.; Venugopalan, P. *J. Am. Chem Soc.* **2002**, *124*, 6530−6531. (b) Thalladi, V. R.; Nusse, M.; Boese, R. *J. Am. Chem. Soc.* **2002**, *124*, 6530−6531. (c) Kobayashi, K.; Shikahara, T.; Horn, E.; Furukawa, N. *Tetrahedron Lett.* **2000**, *41*, 89−93. (d) Jetti, R. K. R.; Xue, F.; Mak, T. C. W.; Nangia, A. *Perkin Trans. 2* **2000**, 1223−1232. (e) Holy, P.; Zavada, J.; Cisarova, I.; Podlaha, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 381−383.

(11) Pérez, C.; Rodríguez, M. L.; Foces-Foces, C., Pérez-Hernández, N.; Pérez, R.; Martín, J. D. *Org. Lett.* **2003**, *5*, 641−644.

(12) Febles, M.; Pérez, C.; Foces-Foces, C.; Rodríguez, M. L.; Pérez-Hernández, N.; Morales, E. Q.; Martín, J. D. *Org. Lett.* **2004**, *6*, 877−880.

(13) For a recent computer simulation study, see: ten Wolde, P. R.; Chandler, D. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 6539−6543.

SCHEME 1. Retrosynthetic Pathways: Routes A and B Planned for the Synthesis of Compounds Possessing Alkyl (Route A) and Alkenyl or Alkynyl (Route B) Appendages



cyclizations to give **1a** occur in a straightforward manner during acidification with 3% HCl of the basic aqueous solution containing crude **2a**. This method allows direct isolation of **1a** by shaking with an organic solvent, dispensing with the isolation of the epoxy alcohol intermediate. Following this methodology, more than 20 homologues of general structure **1a** were synthesized, starting from **5a** in three steps in a 60−80% overall yield.

Our aim in this work is to synthesize molecules that have functionalized R and R′ in different oxidation states. Our purpose is to study solid-state porous structures that can be formed by the incorporation of water molecules in the crystalline structures. From the synthetic point of view, the preparation of these molecules is a complex problem, particularly those that are the smallest in size, in which oxygen atoms are located at R and R′ appendages of two or three carbon atoms. The molecules would be highly oxidized rendering it difficult for each of the oxygenated functions existing therein to be performed independently. Moreover, the protection/deprotection would be difficult to control in each of the functions since their close proximity could lead to intramolecular participation. Our objective is to synthesize compounds that possess alkenyl and alkynyl appendages, leaving the interconversion of these unsaturated carbon functions into oxygenated functions as the final stage of the synthesis.

Introduction of oxygenation at the ketone or hydroxyl oxidation state from alkenes and alkynes is a useful way to introduce complex functionality to end the synthesis. The use of C−C unsaturation for the installation of oxygenation can reduce the reliance on protecting-group manipulation, thereby improving synthetic efficiency.

Synthetic Rationale. The synthesis of structures when R and R′ are alkenyl or alkynyl appendages requires a profound revision of the general strategy utilized until now. We describe it in a retrosynthetic expression as route B and analyze it jointly with route A in Scheme 1.

First, the condensation between carboxylic acid and the corresponding ketone is no longer a good synthetic reaction when the carbonylic function of the ketone becomes conjugated to double and triple bonds. The disconnection cannot be made between the C1 that sustains the carboxylic function and the carbinolic C1′. The structural simplification would have to be carried out between the carbinolic C1′ and the R and R′ appendages, as shown in structure **4b**. This approach leads to esters of diacid 3-methylenecyclohexanedicarboxylic acid **5b** as the common starting material of the synthesis. It is to be expected that the carbonyl group resulting from monoalkenylation or monoalkynylation of one of the ester groups is more electrophilic than the carbonyl of the carboxylate not undergoing attack in this first reaction, to give hydroxyl-esters of the **4b** type. The R and R′ groups could thus be introduced sequentially.

Second, hydrolysis of the ester **4b** to lead the synthesis through the iodolactone, in homology with route A, must not be an efficient reaction. Hydrolysis of **4b**, independently of the acid or medium base in which it is performed, should bring about favorable fragmentation $C_1-C_{1'}$ giving place to the dialkenyl or dialkynyl-ketone and 3-methylenecyclohexanecarboxylic acid. The synthetic route, in this case, cannot be led through the iodolactone. The solution to this problem may be the generation of intermediate oxolane compounds by means of iodination-induced cyclizations (**3b**) or epoxidation (**3′b**) followed by cyclization of the epoxide to give **2b**. The functional interconversion $-CH_2I/-CH_2OH$ (**3b** → **2b**) would be the common nexus of both strategies and lead by hydrolysis of the ester to the required hydroxyl acid **1b**.

A third and very important consideration is that compounds **1b** where R′ and R″ are alkenyl or alkynyl radicals are not the final products of the synthesis. These functions have to be interconverted into diverse oxygenated functions and therefore have to be prepared on a gram scale. That is, the synthetic route has to be operative on a macroscale in order to afford a final

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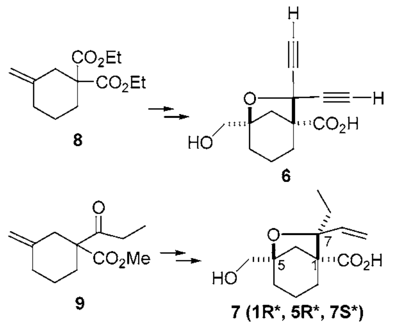
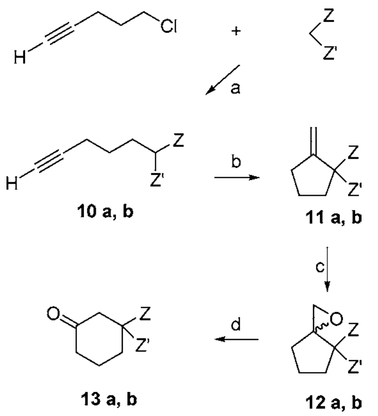
(14) As an example where a mixture of 6-endo-tet and 5-exo-tet cyclyzation compounds was achieved, see: Rodríguez, M. L.; Febles, M.; Pérez, C.; Pérez-Hernández, N.; Martín, J. D.; Foces-Foces, C. *Acta. Crystallogr., Sect. C* **2005**, *61,* 138−142.

SCHEME 2. Chemical Structures of Compounds Prepared in This Study[a]



[a] Details of the chemical synthesis are described in the text.

SCHEME 3. Synthesis of Compounds 10a−13a and 10b−13b[a]



10 a - 13 a, Z = COEt, Z' = CO_2Me
10 b - 13 b, Z = Z' = CO_2Et

[a] Conditions: (a) NaH (0.9 equiv), KI (0.4 equiv), THF/DMF (1:1), reflux, 24 h, **10a**, (84.2%), **10b** (97%); (b) CuI (0.2 equiv), *tert*-BuOK (0.3 equiv), THF, 48−50 °C, 12 h, **11a** (63.2%), **11b** (80%); (c) MCPBA (1.2 equiv), CH_2Cl_2, 25 °C, 3 h, **12a** (97.4%), **12b** (93.4%); (d) LiI (0.2 equiv), CH_2Cl_2, 25 °C, 4 h, **13a** (78%), **13b** (79.4%).

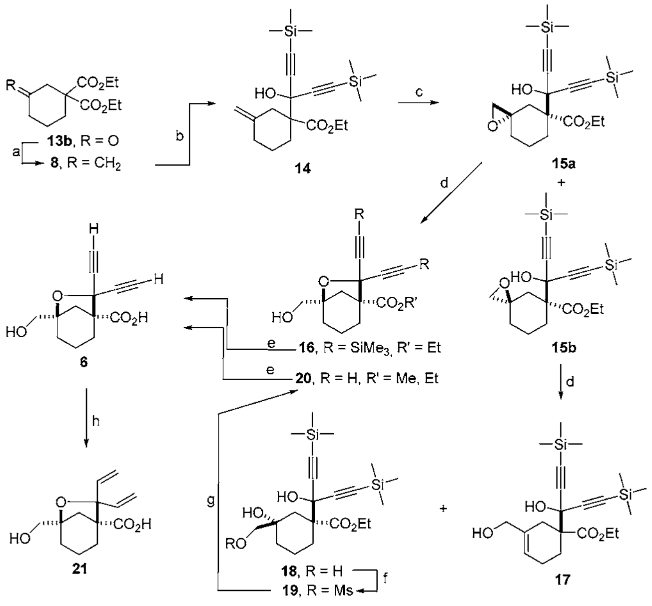
amount sufficient to prepare an extensive family of oxygenated homologues for their study in the solid state.

Results and Discussion

To exemplify the initial concepts involved in these syntheses, we detail here the construction of two homologues , one that possesses two identical acetylene substituents (**6**), and another that includes ethyl/vinyl appendages (**7**) (Scheme 2). Our initial target became the independent synthesis of precursors **8** and **9**, respectively, in gram quantities.

I. Synthesis of Intermediates 13a and 13b. The functionalized cyclohexanones **13a** and **13b** were synthesized following the same protocol (Scheme 3). The synthesis of active methine compounds bearing a 4-alkynyl group used in our study, compounds **10a** and **10b**, were easily prepared in good yields by alkylations of enolates of methyl propionyl acetate and diethylmalonate, respectively, with 5-chloro-1-pentyne[15] (Scheme 3). The enolates were formed by addition of NaH (0.9 equiv), and the reaction was conducted under Ar by addition of KI (0.4 equiv) and refluxing for 24 h. A 1/1 mixture of dry THF/DMF was used as solvent.

SCHEME 4. Synthesis of Compound 6 from 13b[a]



[a] Conditions: (a) $CH_3P^+ Ph_3Br^-$ (1.4 equiv), *t*-BuOK (1.4 equiv), toluene, 0 °C, 2 h (78%); (b) $Me_3SiC≡CH$ (2.0 equiv), *n*-BuLi (2.0 equiv), −78 °C to −15 °C, 30 min, 0 °C, 3 h, THF (86.3%); (c) MCPBA (1.2 equiv), CH_2Cl_2, 25 °C, 1 h, (96%); (d) PTSA (cat.), CH_2Cl_2, −78 °C, 30 min, −15 °C, 30 min → **16** (35.8%) + **17** (7.1%) + **18** (52.9%); (e) saturated aqueous $Ba(OH)_2$, 50 °C, 24 h (100%); (f) MsCl (3.0 equiv), Et_3N (10.0 equiv), CH_2Cl_2, −40 °C, 2 h; (g) K_2CO_3 (4.0 equiv), MeOH, 25 °C, 30 min (99%, two steps); (h) H_2, Lindlar catalyst, EtOAc, 2 h (98%).

Although several strategies have been successfully employed for the cyclization of active methine compounds bearing a 4-alkynyl group to functionalized methylenecyclopentanes (Conia-ene reaction[16]), the high temperature needed severely limits its synthetic utility.[17] Transition metal-catalyzed versions of this reaction[18] operate at lower temperatures, although they require enolate generation,[19] strong acid,[20] or photochemical activation.[21] A catalytic version of the Conia-ene reaction that proceeds at 30 °C in the presence of copper (I) iodide[19c] was the one selected for our synthetic purposes. We investigate the gram-scale copper-catalyzed cyclization of compounds **10a** and **10b**. These compounds were stirred in THF under Ar at 48−50 °C (external oil-bath temperature) in the presence of *t*-BuOK (0.3 equiv) and CuI (0.2 equiv) for 12 h. Under these conditions, methylenecyclopentanes **11a** and **11b** were produced in 63.2% and 80% yields, respectively. Epoxides **12a**, as a 1:1 mixture

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[15] Fournet, G.; Balme, G.; Gore, J. *Tetrahedron* **1991**, *47*, 6293−6304.

[16] For a review see: Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1−19.

[17] For recent publications, see: (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526−4527. (b) Pei, T.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290−11291. (c) Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 2056−2057. (d) Gao, Q.; Zheng, B.-F.; Li, J.-H.; Yang, D. *Org. Lett.* **2005**, *7*, 2185−2188.

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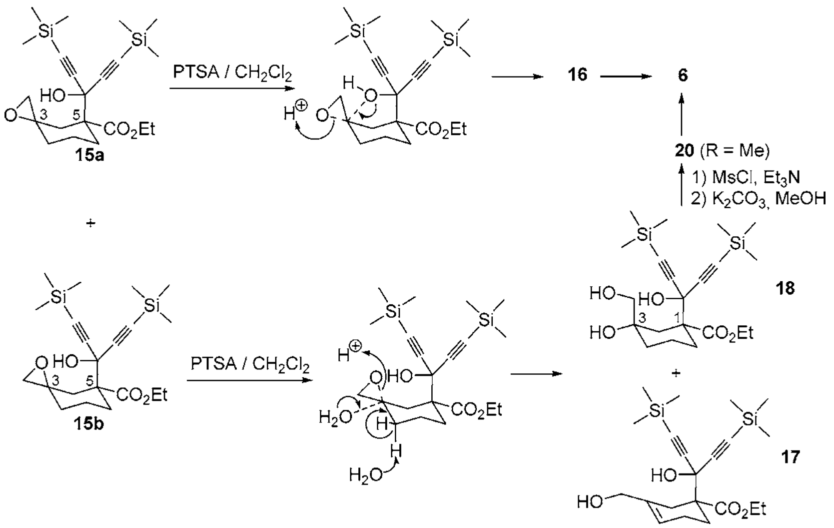
[19] Pd-catalyzed: (a) Balme, G.; Bouyssi, D.; Faure, R.; Gore, J.; van Hemelryck, B. *Tetrahedron* **1992**, *48*, 3891−3902. Mo-catalyzed: (b) McDonald, F. E.: Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691−7692. Cu-catalyzed: (c) Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1297−1300. Ti-catalyzed: (d) Kitagawa, O.; Suzuki, T.; Inoue, T.; Watanabe, Y.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 9470−9475.

[20] Hg/H^+-catalyzed: Boaventura, M. A.; Drouin, J.; Conia, J. M. *Synthesis* **1983**, 801−804.

[21] Co/$h\nu$-catalyzed: (a) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699−2708. (b) Cruciani, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 6677−6680. (c) Renaud, J.-L.; Aubert, C.; Malacria, M. *Tetrahedron* **1999**, *55*, 5113−5128.

SCHEME 5. Pathway for the Epoxide Inversion to Give Compound 6



of diastereomers, and **12b** required for the next reaction were readily prepared in excellent yields by epoxidation (MCPBA, CH_2Cl_2, 25 °C, 3 h) of methylenecyclopentanes **11a** and **11b**, respectively.

Recently, it has been published[22] that a variety of oxaspiroheptanes of general structure **12** can easily be transformed in good to excellent yields into cyclohexanones **13** by treatment with lithium iodide in dichloromethane. We decided to research the macroscale synthetic application of this reaction. We found that gram quantities of epoxides **12a** and **12b** can rearrange into the enlarged cyclohexanones **13a** and **13b** in isolated compound yields of 78% and 79.4%, respectively. The reaction conditions used were the following: addition of 0.2 equiv of LiI to the corresponding solution of **12a** or **12b**, in dichloromethane, at 25 °C. After 3 h under Ar, the reaction was completed in both cases. These mild conditions allow the preparation of **13a** and **13b** as the only isolable compounds. No decarboxylative reactions were observed in any case. In summary, compounds **13a** and **13b** were synthesized, using low-cost materials, in four steps and in multigram amounts, in 40% and 57% overall yields, respectively.

II. Synthesis of Compound 6. II.a. Epoxide-Induced Intramolecular Cyclization Approach. We have accomplished the synthesis of the target molecule **6** by intramolecular attack of hydroxyl groups on epoxides to construct the oxolane ring stereoselectively. The synthetic sequence is outlined in Scheme 4.

To carry out the synthesis starting from ketone **13b**, this compound was methylenated using either Lombardo−Takai[23] or Wittig conditions to give **8**. Whereas the Lombardo−Takai olefination proceeded cleanly and without detectable unwanted reactions, although requiring a large excess of reagent, which made workup and isolation of **8** difficult, Wittig olefination was trouble-free especially when large amounts of compound **8** were required. It was expected that double alkynylation of diester **8** would proceed smoothly to the formation of the dialkynyl derivative **14**. The keto/ester intermediate in the reaction contains a highly electrophilic ketone and, in competition, should be attacked preferentially at the ester group by the second equivalent of acetylide.[24] Thus, compound **14** was obtained in 86% yield by treatment of compound **8** with 2.0 equiv of $Me_3SiC{\equiv}CH$/*n*-BuLi in THF. The requisite epoxide **15a** with favorable stereochemistry for intramolecular attack of the hydroxyl group could not be obtained in pure form. Epoxidation with MCPBA gave in 96% yield an inseparable mixture of epoxides **15a**/**15b** in a 2:3 ratio, the less desirable isomer **15b** being the major component of the mixture. Even though the intramolecular hydroxyl/epoxide cyclization of the epoxide mixture was carried out at −78 °C in CH_2Cl_2 as solvent and a catalytic amount of hydrated *p*-toluenesulfonic acid was used, this reaction gave the required cyclized compound **16** (35.7%), a small amount of the allylic alcohol derivative **17** (7.7%), and triol **18** (52.9%). Longer reaction times, higher temperatures, larger amounts of catalyst, or an anhydrous catalyst, or the use of other acids reduced the yields of **16** and **18** in favor of **17**. Triol **18** was in turn converted to the required epoxide **15a** by selective mesylation of the primary hydroxyl group, which was performed at −40 °C. Crude **15a** was exposed to hydrochloric acid during the extraction procedure to yield cyclized **20** as a mixture of methyl/ethyl esters (99% yield over two steps). A detailed study of the hydroxyl-epoxide intramolecular cyclization is outlined in Scheme 5, where the entire process including the interconversion of epoxides **15a**/**15b** is outlined in more detail. Since in cycloalkene **14** the bulkier dialkynyl substituent preferentially adopted an equatorial position, the mixture of epoxides **15a** and **15b** was thus enriched in the less interesting epimer **15b**, which was hydrated in the acid catalysis to give the triol **18**. However, inversion of configuration at C3 in epoxide **15b** to give **15a** via the triol **18** not only supported the stereochemical assignment for the C3 carbinol in **18**, but also provided a facile preparative route to overcome the unfavorable epoxidation diastereoselectivity. Although the synthetic sequence increased by two steps, the yield and stereoselectivity of epoxide inversion were practically quantitative. Thus, this hydroxylation−inversion protocol represented a reliable and useful method for the synthesis of compound **6**. Esters **16** and **20** were treated with saturated aqueous $Ba(OH)_2$ to give the target hydroxyl acid **6** in pure form. Chromatographic purification was not required

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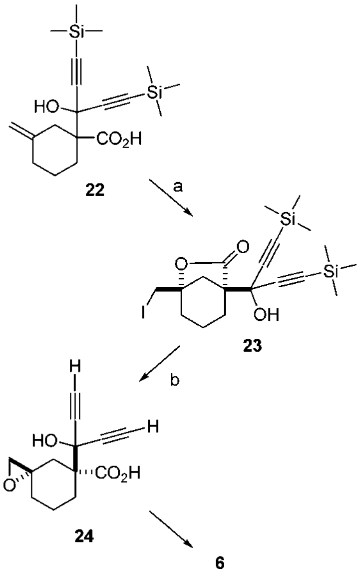
[23] (a) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293−4296. (b) Oshima, K.; Takai, K.; Nazaki, H. *Tetrahedron Lett.* **1978**, *35*, 2417−2420.

[24] For a recent reference, see: Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451−3453.

SCHEME 6. Alternative Synthesis of 6[a]



[a] Conditions: (a) DIPA, I_2, CH_2Cl_2; (b) THF; KOH.

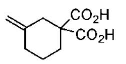
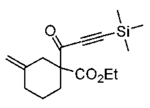
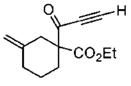
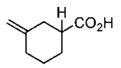
since the compound is highly crystalline and was directly purified by crystallization from CCl_4/Et_2O or MeOH. Partial hydrogenation of **6** using Lindlar catalyst gave the divinyl derivative **21**.

In summary, the compound **6** was synthesized from ketone **13b** on a gram scale, following the epoxide sequence described in Scheme 4. The overall yield was 64% in eight steps, including epoxide interconversion.

II.b. Iodine-Induced Cyclization Approach. An alternative synthesis of compound **6** is described in the Scheme 6. An attempt was made to prepare the hydroxyl acid **22** by base hydrolysis of the hydroxyl ester **14**. It was expected that, following the synthetic sequence outlined in the Scheme 6 and, in consonance with previous results,[8] treatment of the diisopropylamine salt of **22** with iodine in CH_2Cl_2 should give iodolactone **23**. Compound **23** by further reaction with aqueous KOH would produce, via epoxide **24**, the required target molecule **6**. This sequence reduces the number of synthetic steps. However, all attempts to isolate **22** by base hydrolysis of **14** proved unsuccessful. Table 1 includes base hydrolysis results, in mild conditions, of some intermediates prepared in this work. No decarboxylative reactions were observed; however, compound **14** is fragmented to give the corresponding dialkynyl ketone and 3-methylenecyclohexanecarboxylic acid (**28**) in almost quantitative yield. Although these results preclude application of Scheme 6 as a valid approach to the synthesis of compound **6**, they provides an explanation for the unfavorable preparation of **22** via the reverse reaction, that is, the direct condensation of the dilithium salt of **28** with a disilylated 1,4-pentadiyne-3-ketone derivative. In fact, in our hands, this reaction failed for any related coupling using α,*β*-unsaturated ketones.

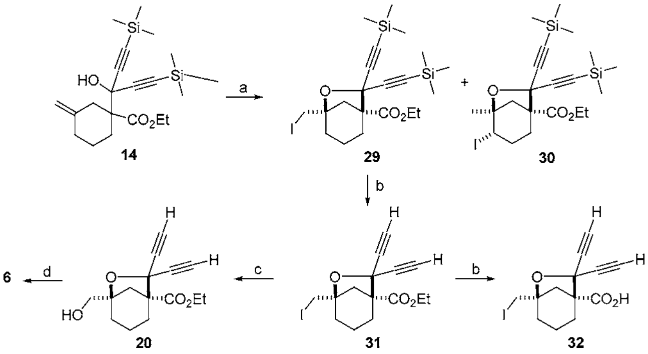
An alternative reaction sequence is outlined in Scheme 7. Treatment of compound **14** with iodine in CH_2Cl_2 in the presence of $NaHCO_3$ yielded the iodo-ether **29**. Reaction of **29** with aqueous saturated solution of $Ba(OH)_2$ gave, after 48 h at 50 °C, a clean mixture of compounds **31** and **32**. No I/OH exchange was observed, even when the reaction was allowed to stand at 50 °C for a week or more, or when the temperature of the reaction was increased to 80−90 °C. Under these latter conditions acid **32** was the only compound isolated.

TABLE 1. Base Hydrolysis of Compounds 8, 14, and 25

Entry	Compound	Hydrolysis[a]	Yield
1	**8**	 **25**	98.8%
2	 **26**	 **27**	96%
3	**14**	 **28**	89.3%

[a] Conditions: saturated aqueous $Ba(OH)_2$, 50 °C, 24 h.

SCHEME 7. Alternative Sequence for 6[a]



[a] Conditions: (a) I_2 (1.5 equiv), $NaHCO_3$, CH_2Cl_2, 25 ° C, 3 h, **29** (72%), **30** (0.6%); (b) saturated aqueous $Ba(OH)_2$, 50 °C, 48 h, **31** (41.5%), **32** (55%); (c) KO_2 (4.5 equiv), 18-crown-6-ether (0.5 equiv), DMSO, 25 °C, 2 h, (10%); (d) saturated aqueous $Ba(OH)_2$, 50 °C, 12 h (100%).

With the available large amount of **29**, we attempted to find mild processes to replace the iodine atom by oxygen, using several of the methods developed over the years as nucleophilic sources of oxygen functionalities.[25] Unexpectedly, when **29** was treated with peracids,[25c−e] or utilizing combinations of phase-transfer reagents, using polar aprotic solvents and water to dissolve and enhance the nucleophilicity of oxygenated anions,[25b] no I/OX exchange products were observed. Instead, no reaction took place or, after long treatments, nonstudied mixtures of compounds that retain the iodine atom were obtained. In contrast, effective exchange was achieved to give **20**, by using a large excess of powdered potassium superoxide and 18-crown-6-ether in dry DMSO under argon at room temperature, followed

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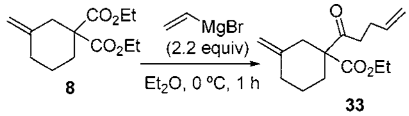
(25) Halogen/hydroxyl interchange induced by hydroxide: (a) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; p 370. (b) Hutchins, R. D.; Taffer, I. M. *J. Org. Chem.* **1983**, *48*, 1360−1362. Peracids: (c) Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888−4889. (d) McDonald, T. L.; Narasimhan, N.; Burka, L. T. *J. Am. Chem. Soc.* **1980**, *102*, 7760−7765. (e) Davidson, R. L.; Kropp, P. J. *J. Org. Chem.* **1982**, *47*, 1904−1909. Superoxide: (f) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, 3183−3186. (g) San Filippo, J., Jr.; Chern, C.-L.; Valentine, J. S. *J. Org. Chem.* **1975**, *40*, 1679−1680. (h) Johnson, R. A.; Nidy, E. G. *J. Org. Chem.* **1975**, *40*, 1680−1681. (i) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1975**, 658−659.

SCHEME 8. Addition of 2.2 Equiv of Vinylmagnesium Bromide to Diester 8



by a cautious addition of saturated aqueous sodium chloride.[25f−i] Compound **20** was quantitatively hydrolyzed to the hydroxyl acid **6** by further treatment with saturated aqueous $Ba(OH)_2$ solution. Unfortunately, conversion of **29** or **31** to compound **20** is a slow reaction, and polymerization of the alkynyl moieties occurs, which is a resource-wasteful competitive reaction and has a deleterious effect on the overall yield. ***Caution**: Potassium superoxide reacts rapidly with water, producing peroxide, hydroxide, and oxygen.*[26] In our experiments, excessive contact with atmospheric moisture was avoided by quickly covering the KO_2 powder with dry solvent. More rigorous anhydrous conditions could be attained in a drybox. In any case, special care should be taken to avoid reaction of large amounts of KO_2 with water in the presence of organic materials,[27] this being a strong limitation of this reaction for our large-scale synthetic purposes.[28]

III. Synthesis of Compound 7 and Related Compounds. III.a. Iodine-Induced Cyclization Approach. Double addition of vinylmagnesium bromide to diester **8** gave the γ,δ-unsaturated ketone **33** as the major component of the mixture. Unavoidable Michael addition occurs in preference to carbonyl addition over the first formed α,β-unsaturated ketone (Scheme 8).

However, synthesis of compound **7** possessing a vinyl appendage was successfully achieved starting from diketone **13a** (Scheme 9). Protection of the C_3-keto group in **13a** (98%), followed by addition of vinylmagnesium bromide and subsequent hydrolysis of the ketal, gave the vinyl carbinol **36** (58%, two steps) as a 1:1 mixture of diastereomers. All attempts to prepare the methylene derivative **37** by Wittig or related olefination methods from **36** were unsuccessful. Instead, fragmentation occurred to give the methyl ester of 3-methylenecyclohexanecarboxylic acid as the only isolable compound. Attempts to prepare **37** from **36** met with complete failure under a wide variety of conditions, clearly because of the great ease of retroaldol cleavage of the same carbon−carbon bond that was involved in the conversion of **14** to the undesired product **28**. However, compound **37** could be easily prepared by direct Wittig olefination of diketone **13a** to give **9** (44%), followed by vinylation of the remaining ketone to yield **37** (74%) as an inseparable 1:1 mixture of diastereomers.

Iodine-induced cyclization of the mixture **37** gave the iodoethers **38a** and **38b** (72%). Treatment of the **38a,b** mixture with potassium superoxide (6.0 equiv), 18-crown-6-ether (0.5 equiv) in DMSO (25 °C, 8 h) gave a mixture of acids from which the required diastereomers **39**-(1*R**,5*R**,7*S**) and **7**-(1*R**,5*R**,7*S**) were isolated by column chromatography and purified by fractional crystallization. The structure and stereochemistry of both compounds were determined by spectroscopic data in combination with X-ray analysis. Our interest in the synthesis of the diastereomer **7**-(1*R**,5*R**,7*S**) is motivated by the expectation that the exchange of the vinyl appendage to give oxygenated functions should occur without interference of the carboxylic acid. The vinyl/hydroxyl or carbonyl conversion of the non depicted diastereomer **7**-(1*R**,5*R**,7*R**) should produce a highly stabilized lactone or hemilactal, respectively, which precludes the formation of the hydroxyl acid H-bonding pattern in crystalline state, one of the main purposes of this synthesis.

In summary, in this preliminary study compound **7** was prepared from diketone **13a** in four steps. Further application of this methodology to an improved synthesis of **7** and other homologues for studies in solid state is currently underway in our laboratory.

III.b. Bis-epoxide Cyclization Approach. We outline here our studies on the synthesis of bis-epoxides **41** starting from diene **40** and their possible application in the synthesis of our target molecule **7** including, instead of a vinyl, a hydroxymethyl appendage (**42**) (Scheme 10). Diene **40** was prepared from the corresponding diketone **13a** by Wittig reaction. Compound **40** is highly volatile, which is an added problem to its isolation (see the Experimental Section) and the main reason for the low yield, 46% in the best case. Treatment of diene **40** with a CH_2Cl_2 solution of MCPBA (2.5 equiv, 25 °C, 3 h) resulted in a smooth sequential epoxidation of the more electrophilic C_3-methylene (first) and the $C_{1'}$-methylene (second) in **40**, leading to a 1:9 mixture of the diastereomeric bis-epoxides **41a**-(1*R**,3*S**,1′*S**)/**41b**-(1*S**,3*S**,1′*S**), **41c**-(1*S**,3*R**,1′*S**), **41d**-(1*R**,3*R**,1′*S**), and the already cyclized benzoate **43**, in a combined yield of 58.2% (Scheme 11). Diastereomer **41a** could be separated from the mixture **41b−d** by chromatography and, kept in a refrigerator, was stable for long periods. Benzoate **43** was isolated as the more polar component of the epoxidation mixture.

The stereochemical structure of the benzoate **43** was established by spectroscopic data in combination with an X-ray analysis and is assumed to result from a S_N2 cyclization of the bis-epoxide **41a** during the epoxidation process.[29] Thus, a longer epoxidation time of diene **40** (20h) under the conditions above-described gave the inseparable mixture of bis-epoxides **41b−d** and benzoate **43** in a 4:3 molar ratio. Only a trace amount of diastereomer **41a** was isolated under these conditions. Furthermore, base hydrolysis of ester functions in **43**, saturated aqueous $Ba(OH)_2$, 50 °C, 12 h, gave the lactone **44**, which was shown to be identical in all respects to the cyclization product achieved by treatment of bis-epoxide **41a** in 20% aqueous THF with TFA (cat.) (0 °C, 30 min) in 52% yield. A hydroxylated homologue (**45**) of lactone **44** was prepared by condensation of the dilithium salt of 3-methylenecyclohexanecarboxylic acid with 2,2-dimethyl-1,3-dioxan-5-ene following the iodolactone sequence depicted in Scheme 1 as route A.[14] In contrast, treatment of the mixture of bis-epoxides **41b−d** with TFA under the same conditions as described above (0 °C, 15 min) was less selective, no identifiable cyclization products being formed. Acetylation of the reaction

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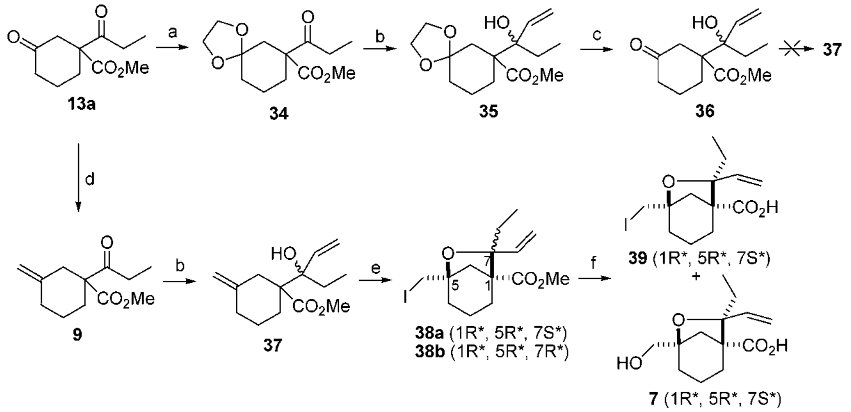
[26] Dietz, R.; Forno, A. E. J.; Larcombe, B. E.; Peover, M. E. *J. Chem. Soc. B* **1970**, 816−820.

[27] Precautions similar to those used with hydrogen peroxide are recommended: *Kirk-Othmer Encyclopedia of Chemical Technology*, 2nd ed.; Wiley: New York, 1967; Vol. 14, pp 748−749, 762−764.

[28] Peroxides and hydroperoxides can be visualized on silica gel TLC plates by spraying with a freshly prepared (remains effective for about 1 day) solution of ammonium thiocyanate (0.625 g), concentrated sulphuric acid (0.125 mL), and ferrous ammonium sulfate (0.875 g) in water (12.5 mL). With this spray, peroxidic materials give a rust-red-colored spot: Mair, R. D.; Hall, R. T. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1971; Vol. II, pp 553−560.

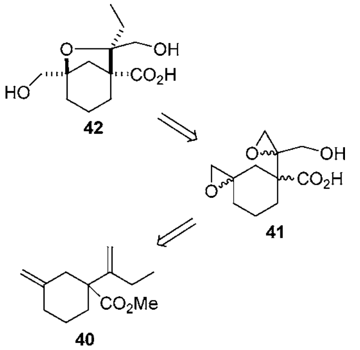
[29] Chlorobenzoic acid byproducts cause acid cyclization specifically on the bis-epoxide **41a**. Buffering the oxidation with $NaHCO_3$ clearly eliminates this cyclization with concomitant increase in the yield of compound **41a** (see the Experimental Section).

SCHEME 9. Synthesis of Compound 7 from 13a[a]

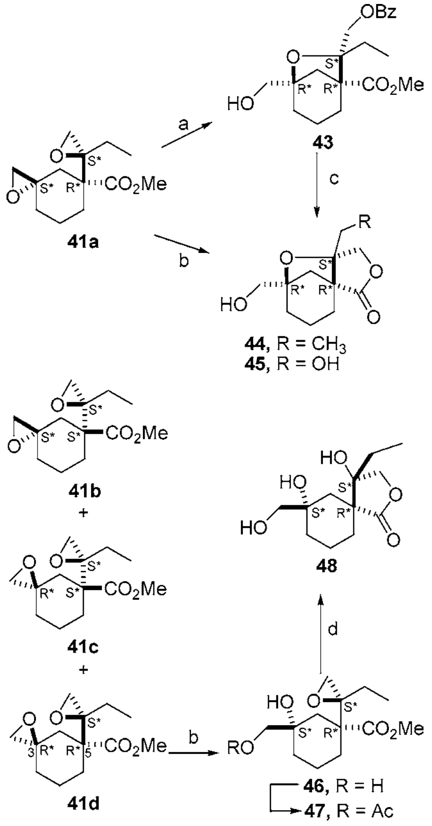


[a] Conditions: (a) $(CH_2OH)_2$ (1.5 equiv), CSA cat., benzene, reflux, 4 h (90%); (b) vinylmagnesium bromide (1.5 equiv), Et_2O, 0 °C, 1 h (74%); (c) 5% HCl (aqueous solution), THF, 25 ° C, 24 h (78.3%); (d) CH_3P^+ Ph_3Br^- (1.4 equiv), *tert*-BuOK (1.4 equiv), toluene, 0 °C, 2 h (43%); (e) I_2 (1.5 equiv), $NaHCO_3$, CH_2Cl_2, 25 ° C, 12 h (72%); (f) KO_2 (6.0 equiv), 18-crown-6-ether (0.6 equiv), DMSO, 25 ° C, 8 h, column chromatography, **39** (24%), **7** (13%).

SCHEME 10. Retrosynthetic Pathway Planned for the Synthesis of Compounds Possessing Hydroxymethyl Appendages via Bis-epoxide Cyclization



SCHEME 11. Bis-epoxide Cyclization Products[a]



[a] Conditions: (a) Chlorobenzoic acid (byproduct in the epoxidation reaction), CH_2Cl_2, 20 h; (b) (i) 20% aqueous THF, TFA cat., 0 °C, 15−30 min, (ii) Ac_2O (5.3 mmol), DMAP cat., Et_3N (4.0 mmol), CH_2Cl_2, 25 °C, 2 h, **44** (acetate) (52%, two steps), **47** (43%); (c) (i) aqueous saturated $Ba(OH)_2$, 50 °C, 24 h, (ii) Ac_2O (5.3 mmol) DMAP cat., Et_3N (4.0 equiv), CH_2Cl_2, 25 ° C, 2 h, **44** (acetate) (70%, two steps); (d) aqueous saturated $Ba(OH)_2$, 50 °C, 48 h, **48** (38%).

mixture gave the hydrated monoepoxide **47** (43% yield, two steps). The structure and stereochemistry of **47** were established by an X-ray analysis and are assumed to result from S_N2 hydration of the C_3-methylene epoxide in **41d** to give diol **46**, followed by acetylation of the primary hydroxymethyl alcohol to yield **47**. Base treatment of **47** with a saturated aqueous Ba-(OH_2) solution (50 °C, 48 h) gave lactone **48** in 38% yield. For some reason, cyclization of **41b** to give **42**, similarly to **41a** → **43** conversion, was not observed, nor can we be sure that **41b** is a true component of the bis-epoxide mixture. However, this mixture contains at least three components that we assume are diastereomers **41b**−**d**.

In view of these results, we conclude here our attempts to achieve hydroxyl acid homologues possessing oxygenated appendages via cyclization of bis-epoxide intermediates. Although some of the cyclization products proved promising, highly stable γ-lactones is always formed, which constitutes a considerable handicap for a rapid synthesis of the required compounds.

IV. X-ray Crystallography. A common feature of the crystal analysis is that all compounds crystallize as anhydrous, and the O−H···O hydrogen bonds are responsible for the supramolecular assembly of the molecules. The molecular structure and supramolecular arrangement of compounds **6**, **7**, and **21** are represented in Figures 2−4. The main distinguishing structural features between compounds **6**, **7**, and **21** lie in the conformation of the hydroxyl group and in the hydrogen-bonding network (Figures 2−4). At the supramolecular level, the hydroxyl group acts only as donor in **6** while in **7** and **21** it acts as both donor and acceptor of hydrogen bonds, resulting in two types of one-dimensional heterochiral ribbons (1D) in **6** and **7** and in sheets in **21** (2D). In the crystal structure of **6**, gauche conformation, the chain is formed by centrosymmetric carboxylic dimers connected by pairs of hydroxyl-to-ether contacts in an alternative tail-to-tail and head-to-head manner (Figure 2). It is noteworthy

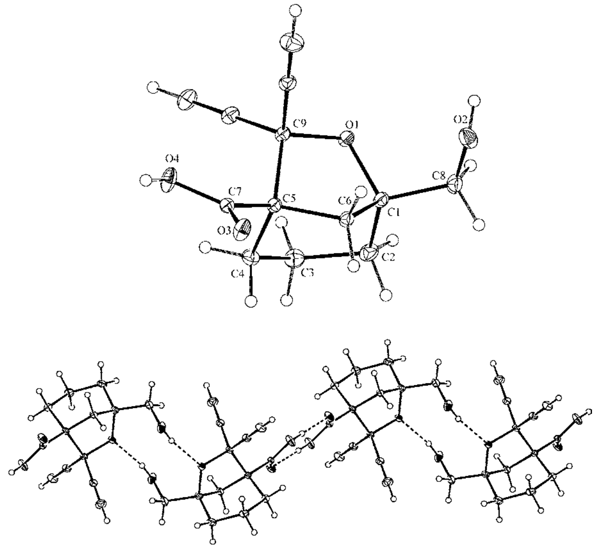


FIGURE 2. Molecular and secondary structure of **6** showing the carboxylic dimeric association and the linkage of the dimers into a chain. O1−C1−C8−O2 = 65.3(1)°, O4−H···O3($1 - x, -y, -z$): 2.629(1), 1.79 Å, 176°. O2−H···O1($1 - x, 1 - y, 1 - z$): 2.846(2), 2.02 Å, 169°.

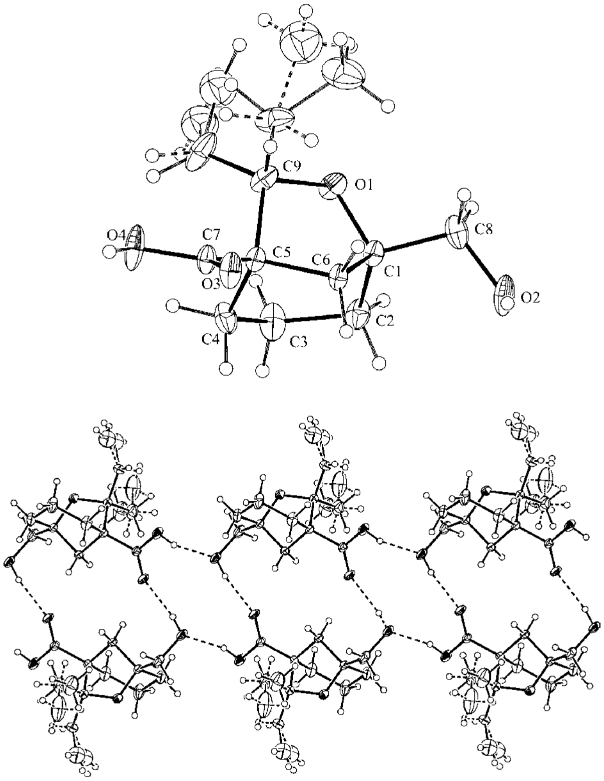


FIGURE 3. Molecular and secondary structure of **7** illustrating the hydrogen-bonding ladder. O1−C1−C8−O2 = −174.2(2)°, O4−H··· O2($1 + x, 1 + y, z$): 2.578(3), 1.76 Å, 164°. O2−H···O3($-x, -y, -z$): 2.721(3), 1.89 Å, 168°.

that no variation has been induced by substitution of one ethyl group for a vinyl one and the structure of **7** is isomorphous with that of the anhydrous analogue **1**-($R_1 = CH_2OH$, R_2 = ethyl).[8a] The hydroxyl group, in anti conformation, acts as the acceptor of one hydrogen bond from the carboxylic acid forming chains generated by translation. These hydrogen bonds are shorter than those between carboxylic acids as in **6**. Centrosymmetricaly related chains, connected through hydroxyl-to-carbonyl hydrogen bonds, form stepladders[30] (Figure 3). In **21**, gauche conformation, the 2D network can be first described as chains of molecules connected by carboxyl-to-hydroxyl bonds, as in **7**, but they are related by 2-fold screw axis instead of by translation with significantly longer bonds. Second, the hydroxyl-to-carbonyl hydrogen bonds are utilized in the assembly of centrosymmetricaly related chains to complete the sheet (Figure 4).

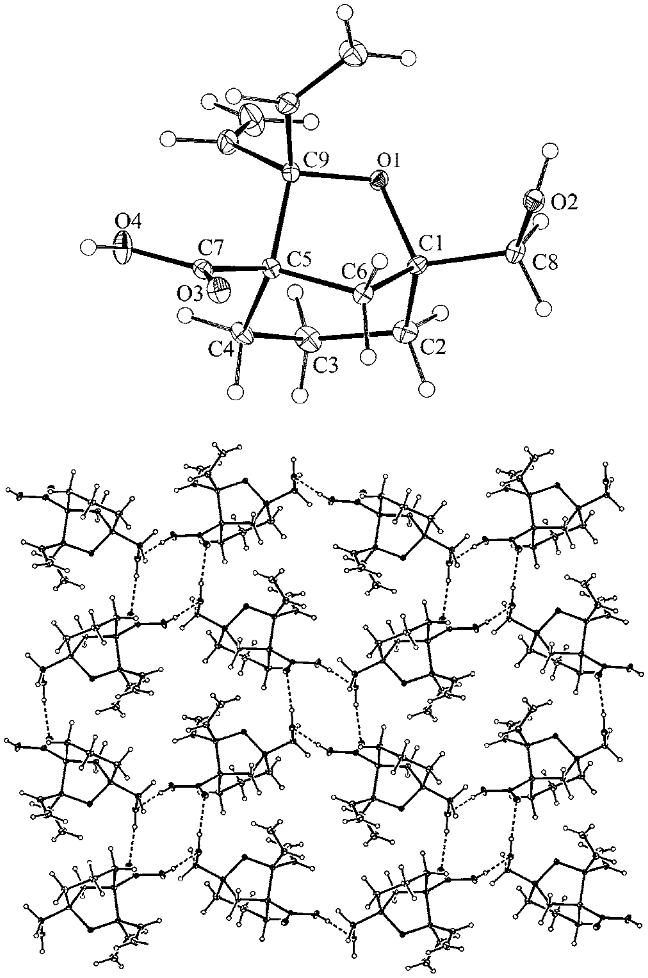


FIGURE 4. Molecular structure and a view of the two-dimesional supramolecular network of **21**. O1−C1−C8−O2 = 69.2(2)°, O4−H···O2($-x, y + {}^{1}/_{2}, -z + {}^{1}/_{2}$): 2.611(2), 1.77 Å, 173°. O2−H···O3($x, -y + {}^{1}/_{2}, z + {}^{1}/_{2}$): 2.767(3), 1.95 Å, 162°.

The type of chains in **7** and of the sheets in **21** have been previously observed in two analogous derivatives with one methyl and one ethyl appendages and with two methyl groups, respectively.[31]

The difference in the hydrogen bond patterns seems to be closely related to the conformation of the hydroxyl group with respect to the ether atom. Conformation anti should give a 1D network, as in **6**, while 1D or 2D should be observed with gauche conformations, **7** and **21**, as pointed out in ref 8a.

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[30] Nguyen, V. T.; Ahn, P. D.; Bishop, R.; Scudder, M. L.; Craig, D. C. *Eur. J. Org. Chem.* **2001**, 4489−4499.

[31] Compounds **1o** and **1q** in ref 8a, respectively.

Conclusions

The present work provides the synthesis of compounds **6** and **7** in 8−10 linear steps, as valuable intermediates for the preparation of a family of highly oxygenated compounds of general structure **1**. The direct alkenyl and alkynyl couplings illustrated here may allow for the facile synthesis of analogues varying in substitution and functionalization. The selective oxygenation of alkenes in processes, such as dihydroxylation, hydration (typically as hydroboration−oxidation), and Wacker-type oxidation,[32] is a successful and pervasive method. Similarly, terminal alkynes have been used to afford carbonyl products available by direct hydration[33] or through the intermediacy of vinylmetal species.

Opportunities to improve upon this route include the enhancement of the CH_2I/CH_2OH interconversion and the development of a more stereoselective annulation process. Nonetheless, the current synthesis provides relative succinct access to compounds of general structure **1**, which include alkenyl and alkynyl appendages. In the crystalline state, the assembly of molecules via O−H···O hydrogen bonds resulted in two types of one-dimensional networks in **6** and **7** and a two-dimensional network in **21**. The absence of the hydroxyl group in the iodide derivatives **32** and **39** led to carboxylic acid dimer formation as the main hydrogen-bonding motif (see the Supporting Information).

Further synthetic and structural studies based on compounds **6** and **7** will be reported in due course.

Experimental Section

General Methods. Unless otherwise noted, all reactions were carried out under argon atmosphere in oven-dried glassware using standard syringe, cannula, and septa techniques. Toluene, diethyl ether, and tetrahydrofuran were distilled from sodium/benzophenone ketyl under nitrogen immediately prior to use; dichloromethane, triethylamine, acetonitrile, dimethyl sulfoxide, and pyridine were distilled from CaH_2. LiBr, LiCl, and LiI were dried by heating at 120 °C for 20 h at ~0.4 torr. Analytical TLC was performed with 0.25 mm EM silica gel 60 F_{254} plates. NMR spectra are referenced to residual $CHCl_3$ at 7.25 (^1H) and 77.0 ppm (^{13}C). The mass spectrometers used show deviations of less than 5 ppm. Melting points are uncorrected.

Typical synthetic sequences are described:

Methyl 2-Propionyl-6-heptynoate (10a). To a stirred suspension under Ar of sodium hydride, 60% dispersion in mineral oil (3.65 g, 90.8 mmol, 0.9 equiv) in dried THF/DMF (1/1) (100 mL), was added anhydrous potassium iodide (6.91 g, 41.1 mmol, 0.4 equiv). This mixture was stirred at 25 °C for 30 min before methyl propionyl acetate (12.5 mL, 99.3 mmol, 1.0 equiv) was slowly added via cannula. The resultant solution was stirred for an additional 15 min, at which time 5-chloro-1-pentyne (8.7 mL, 82.5 mmol, 0.8 equiv) was added over 5 min. The mixture was heated at reflux under Ar for 24 h. The solution was cooled to room temperature, diluted with diethyl ether (100 mL), and washed with aqueous 3% HCl, H_2O, and saturated aqueous NaCl (100 mL each). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 5:1, v/v) to give **10a** (16.42 g, 83.6 mmol, 84.2%) as a clear, colorless oil: R_f 0.70 (hexanes−ethyl acetate, 5:1, v/v); IR (neat) 3289, 1743, 1715, 1458, 1351, 1205, 1113, 967 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.71 (s, 3H), 3.47 (dd, J = 7.3, 7.3 Hz, 1H), 2.58 (dq, J = 18.2, 7.3 Hz, 1H), 2.50 (dq, J = 18.2, 7.3 Hz, 1H), 2.20 (ddd, J = 6.9, 6.9, 2.4 Hz, 2H), 1.98−1.91 (m, 3H), 1.52−1.48 (m, 2H), 1.04 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.9, 170.6, 83.8, 69.4, 58.5, 52.8, 35.6, 27.6, 26.6, 18.6, 8.0; HRMS calcd for $C_{11}H_{15}O_3$ [M − H]$^+$ 195.1021, found 195.1015. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.56; H, 7.99.

Methyl 2-Methylene-1-propionylcyclopentane-1-carboxylate (11a). To a solution of **10a** (16.42 g, 83.6 mmol, 1.0 equiv) in dry THF (100 mL) at room temperature and under Ar were added cooper (I) iodide (3.18 g, 16.7 mmol, 0.2 equiv) and potassium *t*-butoxide (25.1 mmol, 25.1 mL of a 1.0 M solution in THF, 0.3 equiv). The resulting mixture was heated at 48 °C by an external oil bath for 12 h, at which point TLC showed no remaining **10a**. The solution was cooled to room temperature, diluted with dichloromethane (100 mL), and washed with aqueous 3% HCl (50 mL), H_2O (50 mL), and saturated aqueous NaCl (50 mL). The aqueous phases were extracted with dichloromethane (3 × 25 mL), and the combined organic phases dried over $MgSO_4$, filtered, and concentrated to give crude **11a** (10.54 g) as a deep yellow oil. Silica gel column chromatography of the residue (hexanes−ethyl acetate, 10:1, v/v) gave pure **11a** (10.36 g, 52.8 mmol, 63.2%) as a colorless oil: R_f 0.59 (hexanes−ethyl acetate, 10:1, v/v); IR (neat) 3100, 1744, 1716, 1649, 1435, 1343, 1232, 1121, 897 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.22 (dd, J = 2.0, 2.0 Hz, 1H), 5.15 (dd, J = 2.2, 2.2 Hz, 1H), 3.68 (s, 3H), 2.55 (dq, J = 18.0, 7.3 Hz, 1H), 2.44 (dq, J = 18.0, 7.3 Hz, 1H), 2.39−2.35 (m, 2H), 2.34 (ddd, J = 13.5, 6.7, 6.7 Hz, 1H), 2.13 (ddd, J = 13.5, 6.7, 6.7 Hz, 1H), 1.72−1.58 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.5, 171.8, 148.7, 112.0, 70.2, 52.5, 35.1, 33.9, 32.2, 24.1, 8.5; HRMS calcd for $C_{11}H_{15}O_3$ [M − H]$^+$ 195.1021, found 195.1025. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.47; H, 8.06.

(3*R/3*S**,4*R**)-Methyl 4-Propionyl-1-oxaspiro[2.4]heptane-4-carboxylate (12a).** To a solution of **11a** (10.36 g, 52.8 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) magnetically stirred in a 300 mL conical two-necked flask was added dropwise over 30 min a solution of 3-chloroperoxybenzoic acid (15.7 g, 63.5 mmol, 1.2 equiv) in CH_2Cl_2 (120 mL). After the reaction was stirred for 3 h, it was diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl (200 mL each). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 10:1, v/v) to give **12a** (10.91 g, 51.5 mmol, 97.4%) as a 1:1 mixture of epoxides on the basis of integration of the 500 MHz ^1H NMR resonances at δ 1.03 and 0.99, respectively: R_f 0.25 (hexanes−ethyl acetate, 9:1, v/v); IR (neat) 2850, 1744, 1714, 1435, 1347, 1270, 1128, 1009, 946, 903, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.68 (s, 3H), 3.67 (s, 3H), 2.99−2.96 (m, 4H), 2.75−2.67 (m, 1H), 2.66−2.59 (m, 1H), 2.54−2.29 (m, 4H), 2.20−2.11 (m, 3H), 1.97−1.87 (m, 3H), 1.74−1.62 (m, 4H), 1.03 (t, J = 7.0 Hz, 3H), 0.99 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.1, 204.3, 172.0, 168.6, 68.9, 67.3, 65.9, 65.8, 52.5 (2 × C), 50.3, 50.2, 34.1, 33.9, 33.3, 33.2, 33.0, 32.3, 22.9, 22.5, 8.2, 7.5; HRMS calcd for $C_{11}H_{16}O_4$ M$^+$ 212.1048, found 212.1036; calcd for $C_{11}H_{15}O_4$ [M − H]$^+$ 211.0970, found 211.0966. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.95; H, 7.73.

Methyl 3-Oxo-1-propionylcyclohexane-1-carboxylate (13a). To a stirred room-temperature solution of **12a** (10.93 g, 51.5 mmol, 1.0 equiv) in CH_2Cl_2 (120 mL) was added, in five portions, anhydrous lithium iodide (1.38 g, 10.3 mmol, 0.2 equiv). This mixture was stirred for 4 h, at which time TLC showed no remaining **12a**. The resultant pale yellow solution was quenched with saturated aqueous NaCl (100 mL). The separated organic phase was washed with H_2O (2 × 50 mL) and saturated aqueous NaCl (2 × 50 mL). The aqueous phases were extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phases were dried over $MgSO_4$, the residue was filtered through silica gel with hexanes−

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ethyl acetate (5:1, v/v), and the filtrate concentrated to yield diketone **13a** (8.52 g, 40.0 mmol, 78%) as colorless foam. R_f 0.2 (hexanes−ethyl acetate, 5:1, v/v); IR (neat) 1717, 1451, 1352, 1225, 1033, 918 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.72 (s, 3H), 2.66 (d, *J* = 15.0 Hz, 1H), 2.60 (d, *J* = 15.0 Hz, 1H), 2.46 (dq, *J* = 18.1, 7.2 Hz, 1H), 2.41 (dq, *J* = 18.1, 7.2 Hz, 1H), 2.29−2.22 (m, 3H), 2.11 (ddd, *J* = 13.8, 6.9, 6.9 Hz, 1H), 1.80−1.74 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.9, 206.0, 171.8, 62.9, 52.9, 44.9, 39.9, 31.5, 29.4, 21.4, 7.9; HRMS calcd for $C_{11}H_{17}O_4$ [M + H]$^+$ 213.1127, found 213.1126. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: 61.95; H, 7.55.

Diethyl-3-methylene-1,1-cyclohexanedicarboxylate (8). To a room-temperature solution of methyltriphenylphosphonium bromide (10.0 g, 28.6 mmol, 1.4 equiv) in dry toluene (100 mL) was added in one portion potassium *tert*-butoxide (3.14 g, 28.6 mmol, 1.4 equiv). The resulting deep yellow mixture was heated to 90 °C for 2 h and then cooled to 0 °C before a solution of ketone **13b** (4.84 g, 20.0 mmol, 1.0 equiv) in toluene (30 mL) was slowly added via cannula. The resultant solution was further stirred a 0 °C for 2 h, and then an aqueous saturated solution of NH_4Cl (200 mL) was added. The biphasic mixture was extracted with diethyl ether (2 × 100 mL), and the combined organic extracts were dried ($MgSO_4$). Diethyl ether was removed by distillation before *n*-hexane (100 mL) was added, and the solution was left overnight at −20 °C, allowing crystallization of most triphenylphosphine oxide, which was removed by filtration. The solution was washed with H_2O and saturated aqueous NaCl (100 mL each) and then concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 10:1, v/v) to give **8** (3.74 g, 15.6 mmol, 78%) as a clear colorless oil: R_f 0.49 (hexanes−ethyl acetate, 9:1, v/v). A small fraction was purified by bulb-to-bulb distillation under reduced pressure (0.7 torr) at 75 °C; IR (neat) 3075, 1732, 1655, 1448, 1310, 1244, 1101, 896 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.70 (s, 2H), 4.15 (q, *J* = 7.0 Hz, 4H), 2.64 (s, 2H), 2.11−2.07 (m, 2H), 2.03−1.99 (m, 2H), 1.66−1.61 (m, 2H), 1.20 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2 (2 × C), 144.2, 110.5, 61.2 (2 × C), 56.6, 39.6, 33.9, 31.1, 24.1, 14.0 (2 × C); HRMS calcd for $C_{13}H_{21}O_4$ [M + H]$^+$ 241.1439, found 241.1438. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.95; 8.41.

Ethyl 1-[1′-Hydroxy-1′-bis(trimethylsilyl)ethynyl]-3-methylenecyclohexane-1-carboxylate (14). To a stirred −78 °C solution of trimethylsilylacetylene (4.44 g, 45.2 mmol, 6.52 mL, 2.0 equiv) in THF (10 mL) under Ar was added dropwise *n*-butyllithium (28.25 mL, 1.6 M solution in hexanes, 2.0 equiv). The solution was stirred at −40 °C for 30 min. The solution was then cooled to −78 °C, and a solution of diester **8** (5.43 g, 22.6 mmol, 1.0 equiv) in THF (10 mL) was added via cannula. After 15 min at −78 °C, the reaction mixture was allowed to reach −15 °C, and after 30 min allowed to warm to 0 °C. The mixture was further stirred for 3 h at 0 °C, allowed to reach room temperature, diluted with diethyl ether (100 mL), washed with 5% aqueous HCl and saturated aqueous NaCl (50 mL each). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 9:1, v/v) to give **14** (7.62 g, 19.51 mmol, 86.3%) as a crystalline solid: mp 56−57 °C; R_f 0.56 (hexanes−ethyl acetate, 9:1, v/v); IR (KBr) 3380, 3070, 2168, 1714, 1653, 1452, 1300, 1030, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.70 (brs, 2H), 4.41 (s, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 2.84 (d, *J* = 13.5 Hz, 1H), 2.42 (d, *J* = 13.5 Hz, 1H), 2.33−2.25 (m, 2H), 2.03−1.75 (m, 3H), 1.49−1.44 (m, 1H), 1.25 (t, *J* = 7.0 Hz, 3H), 0.20 (s, 9H), 0.18 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3, 145.7, 110.3, 102.6, 102.4, 90.2, 90.0, 70.1, 61.8, 58.0, 38.7, 34.7, 29.7, 25.0, 14.5, 0.1 (6 × C); HRMS calcd for $C_{21}H_{34}O_3Si_2$ M$^+$ 390.2047, found 390.2029. Anal. Calcd for $C_{21}H_{34}O_3Si_2$: C, 64.56; H, 8.77. Found: C, 64.40; H, 8.69.

Preparation of (1*R,5*R**)-Ethyl 5-Hydroxymethyl-7,7-bis-[(trimethylsilyl)-ethynyl]-6-oxabicyclo[3.2.1]octane-1-carboxylate (16), Ethyl 3-Hydroxymethyl-1-[1′hydroxy-1′-bis[(trimethylsilyl)ethynyl]-3-cyclohexen-1-carboxylate (17), and (3*S**,5*R**)-Ethyl 3-Hydroxy-3-hydroxymethyl-1-[1′-hydroxy-1′-bis[(trimethylsilyl)-ethynyl]-cyclohexane-1-carboxylate (18).** To a solution of **14** (8.60 g, 22.1 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) magnetically stirred in a 250 mL two-necked flask was added, dropwise over 25 min, a solution of MCPBA (6.55 g, 26.5 mmol, 1.2 equiv) in CH_2Cl_2 (100 mL). After the reaction was stirred for 1 h, it was washed with saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl (100 mL each). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 9:1, v/v) to give the unstable mixture of epoxides **15a,b** (8.61 g, 21.2 mmol, 96%) as a 2:3 mixture of **15a-(3*S**,5*R**)/15b-(3*R**,5*R**)** on the basis of integration of the 300 MHz ^{1}H NMR resonance signals at δ 2.72 and 2.60, respectively. The mixture of epoxides: R_f 0.2 (hexanes−ethyl acetate, 9:1, v/v) was dissolved in 50 mL of CH_2Cl_2, cooled under Ar at −78 °C, and used in the next experiment without further structural study.

To a stirred −98 °C solution of the mixture of epoxides **15a** and **15b** (8.61 g, 21.2 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) under Ar was added a catalytic amount of *p*-toluenesulfonic acid (6.0 mg) in CH_2Cl_2 (4.0 mL) via syringe over 5 min. After 30 min at −78 °C and stirring for an additional 30 min, saturated aqueous NH_4Cl (50 mL) was added, and the mixture was allowed to reach room temperature. The mixture was diluted with CH_2Cl_2 (25 mL), washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl (100 mL each). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 9:1, v/v) to give, according to the elution from the chromatographic column, compounds **16** (3.11 g, 7.59 mmol, 35.8%), **17** (611 mg, 1.50 mmol, 7.1%), and **18** (4.75 g, 11.21 mmol, 52.9%).

Compound **16**, white solid: mp 64−65 °C; R_f 0.49 (hexanes−ethyl acetate, 3:2, v/v); IR (neat) 3561, 2171, 1722, 1248, 1067, 843, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.08 (dq, *J* = 10.7, 7.2 Hz, 1H), 4.03 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.47 (dd, *J* = 11.9, 2.5 Hz, 1H), 3.37 (dd, *J* = 11.9, 11.5 Hz, 1H), 2.86 (ddd, *J* = 12.0, 2.2, 2.2 Hz, 1H), 2.31 (brddd, *J* = 13.2, 12.5, 2.5 Hz, 1H), 2.13 (ddddd, *J* = 13.2, 13.2, 12.5, 6.5, 6.5 Hz, 1H), 1.98 (dd, *J* = 11.5, 2.5 Hz, 1H), 1.68−1.58 (m, 2H), 1.53 (d, *J* = 12.0 Hz, 1H), 1.50 (brdd, *J* = 13.2, 6.5 Hz, 1H), 1.24 (ddd, *J* = 13.2, 11.0, 6.5 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.12 (s, 9H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 103.2, 99.8, 90.6, 90.0, 86.0, 74.4, 65.2, 60.8, 60.5, 38.1, 31.7, 31.6, 19.1, 13.9, −0.4 (3 × C), −0.5 (3 × C); HRMS calcd for $C_{21}H_{34}O_4Si_2$ M$^+$ 406.1996, found 406.1981. Anal. Calcd for $C_{21}H_{34}O_4Si_2$: C, 62.02; H, 8.43. Found: C, 61.77; H, 8.35.

Compound **17**, colorless foam: R_f 0.31 (hexanes−ethyl acetate, 3:2, v/v); IR (neat) 3437, 3050, 2168, 1729, 1693, 1442, 1250, 1054, 844, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.63 (brs, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.06 (brd, *J* = 14.2 Hz, 1H), 4.00 (brd, *J* = 14.2 Hz, 1H), 2.60 (d, *J* = 17.0 Hz, 1H), 2.43 (d, *J* = 17.0 Hz, 1H), 2.31 (dd, *J* = 13.0, 5.5 Hz, 1H), 2.19 (brd, *J* = 17.9 Hz, 1H), 2.10−2.00 (m, 1H), 1.82 (ddd, *J* = 13.0, 12.5, 6.5 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.15 (s, 9H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.7, 135.9, 121.3, 102.5, 101.7, 89.8, 89.7, 69.3, 67.0, 61.5, 54.8, 30.0, 25.7, 23.0, 14.1, −0.3 (3 × C), −0.6 (3 × C); HRMS calcd for $C_{21}H_{34}O_4Si_2$ M$^+$ 406.1995, found 406.1974. Anal. Calcd for $C_{21}H_{34}O_4Si_2$: C, 62.02; H, 8.43. Found: C, 62.04; H, 8.47.

Compound **18**, colorless foam: R_f 0.14 (hexanes−ethyl acetate, 3:2, v/v); IR (neat) 3428, 2170, 1693, 1250, 1054, 844, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.46 (s, 1H), 4.26 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.14 (dq, *J* = 10.6, 6.1 Hz, 1H), 3.37 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.33 (dd, *J* = 10.8, 4.2 Hz, 1H), 2.60 (s, 1H), 2.52 (dd, *J* = 4.2, 3.0 Hz, 1H), 2.38 (d, *J* = 14.2 Hz, 1H), 2.28 (brd, *J* = 14.0 Hz, 1H), 1.92 (ddddd, *J* = 14.0, 14.0, 14.0, 3.5, 3.5 Hz, 1H), 1.69 (d, *J* = 14.2 Hz, 1H), 1.66−1.56 (m, 3H), 1.29 (t, *J* =

7.1 Hz, 3H), 1.07 (ddd, $J = 13.8, 13.8, 4.0$ Hz, 1H), 0.14 (s, 9H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.4, 102.4, 101.7, 90.4, 89.3, 71.5 (2 × C), 70.1, 61.8, 53.9, 36.8, 33.0, 29.0, 18.2, 14.0, −0.1 (3 × C), −0.3 (3 × C); HRMS calcd for $C_{21}H_{36}O_5Si_2$ M^+ 424.2101, found 424.2079. Anal. Calcd for $C_{21}H_{36}O_5Si_2$: C, 59.39; H, 8.54. Found: C, 59.34; H, 8.63.

(1*R,5*R**)-7,7-Diethynyl-5-hydroxymethyl-6-oxabicyclo[3.2.1]-octane-1-carboxylic Acid (6).** A suspension of compound **16** (244 mg, 0.60 mmol, 1.0 equiv) in a saturated aqueous solution of barium hydroxide (50 mL) was allowed to stand at 50 °C for 24 h. A 5% aqueous solution of HCl was added until the aqueous suspension was acid to pH paper, and then it was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give pure **6** (140.4 mg, 0.60 mmol, 100%) as a crystalline solid: mp 138−140 °C; R_f 0.55 (ethyl acetate); IR (KBr) 3502, 3292, 3180, 2588, 2110, 1704, 1340, 1112, 1055, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.50 (d, $J = 11.8$ Hz, 1H), 3.45 (d, $J = 11.8$ Hz, 1H), 3.09 (s, 1H), 3.00 (s, 1H), 2.68 (ddd, $J = 11.8, 2.0, 2.0$ Hz, 1H), 2.39 (ddd, $J = 11.8, 6.0, 2.0$ Hz, 1H), 2.20 (ddddd, $J = 15.4, 12.8, 11.6, 7.6, 6.0$ Hz, 1H), 1.76−1.68 (m, 2H), 1.72 (d, $J = 11.8$, 1H), 1.60 (brdd, $J = 12.5, 6.0$ Hz, 1H), 1.41 (ddd, $J = 12.8, 12.5, 6.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.7, 85.7, 82.2, 79.1, 74.1, 73.5, 73.2, 66.2, 60.1, 39.2, 31.4, 31.2, 18.9 ; HRMS calcd for $C_{13}H_{14}O_4$ M^+ 234.0892, found 234.0893. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.72; H, 5.95.

(1*R,5*R**)-7,7-Divinyl-5-hydroxymethyl-6-oxabicyclo[3.2.1]-octane-1-carboxylic Acid (21).** The hydroxyl acid **6** (234 mg, 1.0 mmol) was dissolved in ethyl acetate (20 mL), and Lindlar catalyst (32 mg) was added. The reaction was then allowed to stir under an excess of H_2 (balloon pressure). After 3 h the reaction was filtered through a short plug of silica gel, and the silica gel was washed with ethyl acetate (50 mL). The filtrate was concentrated to afford pure **21** (233 mg, 0.98 mmol, 98%) as a crystalline solid: mp 139−140 °C; R_f 0.45 (ethyl acetate); IR (KBr) 3734, 2360, 2342, 1703, 1457, 1402, 1257, 1040, 1004, 928 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.28 (dd, $J = 17.3, 11.0$ Hz, 1H), 5.91 (dd, $J = 17.0, 10.6$ Hz, 1H), 5.52 (dd, $J = 17.3, 1.9$ Hz, 1H), 5.33 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.27 (dd, $J = 11.0, 1.9$ Hz, 1H), 5.14 (dd, $J = 10.6, 1.5$ Hz, 1H), 3.66 (d, $J = 11.7$ Hz, 1H), 3.61 (d, $J = 11.7$ Hz, 1H), 2.55 (ddd, $J = 11.7, 2.2, 2.2$ Hz, 1H), 2.15 (brddd, $J = 15.2, 6.8, 2.1$ Hz, 1H), 2.15−2.05 (m, 1H), 1.80 (brddd, $J = 12.9, 7.2, 1.7$ Hz, 1H), 1.71−1.64 (m, 1H), 1.58 (ddd, $J = 13.9, 7.2, 7.2$ Hz, 1H), 1.50 (d, $J = 11.7$ Hz, 1H), 1.32 (ddd, $J = 12.2, 12.2, 6.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.1, 139.8, 135.5, 115.8, 115.3, 87.0, 83.3, 67.3, 56.3, 38.7, 31.8, 31.2, 17.8; HRMS calcd for $C_{13}H_{18}O_4$, found 238.1200, 238.1205. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.54; H, 7.75.

Preparation of Compound 6 from Triol 18. Methanesulfonyl chloride (928 mg, 8.1 mmol, 0.63 mL, 3.0 equiv) was added to a solution of compound **18** (1.15 g, 2.70 mmol, 1.0 equiv) in CH_2Cl_2 (20.0 mL) and triethylamine (2.73 g, 27.0 mmol, 3.8 mL, 10.0 equiv) at −40 °C. The mixture was stirred at −40 °C for 2 h, and then methanol (2.0 mL) was added to decompose excess MsCl. The mixture was allowed to warm to room temperature, and then it was poured in water (50 mL) and was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide crude mesylate **19**. The crude product was dissolved in methanol (20.0 mL), and potassium carbonate (1.5 g, 4.0 equiv) was added at room temperature. The mixture was stirred at room temperature for 30 min, and then the resulting suspension was poured into water (100 mL) and was extracted with CH_2Cl_2 (3 × 30 mL). Combined extracts containing crude epoxide were added to 0.5 M aqueous HCl (20 mL), and the resulting heterogeneous solution was stirred vigorously at room temperature for 10 min. The organic layer was separated, then was washed with saturated aqueous NaCl (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. After short column chromatography of the residue on silica gel with hexanes−ethyl acetate (1:3, v/v) gave an inseparable mixture of methyl and ethyl esters (**20**) in a 9:1 ratio (707 mg, 2.69 mmol, 99%). After two crystallizations from *n*-hexane/acetone the methyl ester derivative of **20** (R═Me) was purified: mp 107−109 °C; R_f 0.38 (hexanes−ethyl acetate, 2:3, v/v); IR (neat) 3483, 3288, 3188, 2111, 1729, 1435, 1376, 1362, 1281, 1156, 1030, 880, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.74 (s, 3H), 3.59 (dd, $J = 12.1, 3.4$ Hz, 1H), 3.48 (dd, $J = 12.1, 10.2$ Hz, 1H), 2.68 (ddd, $J = 12.0, 2.4, 2.4$ Hz, 1H), 2.72 (s, 1H), 2.62 (s, 1H), 2.42 (ddd, $J = 12.6, 6.8, 2.4$ Hz, 1H), 2.21 (ddddd, $J = 13.2, 13.2, 13.2, 6.8, 6.8$ Hz, 1H), 1.89 (dd, $J = 10.2, 3.4$ Hz, 1H), 1.81−1.69 (m, 2H), 1.67 (d, $J = 12.0$ Hz, 1H), 1.65−1.60 (m, 1H), 1.32 (ddd, $J = 12.2, 12.2, 5.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 86.6, 81.9, 78.7, 74.4, 74.3, 73.7, 65.4, 60.5, 52.3, 39.2, 31.7, 31.6, 19.1; HRMS calcd for $C_{14}H_{16}O_4$ M^+ 248.1049, found 248.1042. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.55; H, 6.62.

The mixture of **20** (R═Me, Et) was treated with a saturated water solution of barium hydroxide, under similar conditions as above indicated for the base hydrolysis of **16**, to give quantitatively pure hydroxyl/acid **6**.

(1*R,5*R**)-Ethyl 5-Iodomethyl-7,7-bis[(trimethylsilyl)ethynyl]-6-oxabicyclo-[3.2.1]octane-1-carboxylate (29) and (1*R**,4*S**,5*S**)-Ethyl 4-Iodo-5-methyl-7,7-bis[(trimethylsilyl)ethynyl]-6-oxabicyclo-[3.2.1]octane-1-carboxylate (30).** Iodine (3.46 g, 13.61 mmol, 1.5 equiv) was added in one portion to a stirred under Ar solution of compound **14** (3.54 g, 9.07 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL). Sodium bicarbonate (50 mg) was added, and the reaction was allowed to stand at room temperature. When monitoring of the reaction by TLC indicated that all starting material has been consumed (ca. 3 h). The reaction mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were shaken with 10% aqueous solution $Na_2S_2O_3$, saturated aqueous NaCl (2 × 50 mL each), dried ($MgSO_4$), filtered, and the organic solvent evaporated in vacuo. The residue was purified by chromatography on silica gel (hexanes−ethyl acetate, 9:1, v/v) to give, according to elution from the chromatographic column, compounds **30** (42 mg, 0.08 mmol, 0.6%) and **29** (5.06 g, 9.79 mmol, 72%).

Compound **29** was isolated as a noncrystalline solid: R_f 0.50 (hexanes−ethyl acetate, 19:1, v/v); IR (neat) 2172, 1736, 1300, 1052, 937, 844, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.16 (dq, $J = 10.0, 7.5$ Hz, 1H), 4.08 (dq, $J = 10.0, 7.5$ Hz, 1H), 3.28 (s, 2H), 2.69 (d, $J = 12.0$ Hz, 1H), 2.30 (brdd, $J = 11.4, 5.0$ Hz, 1H), 2.29−2.18 (m, 1H), 1.82 (d, $J = 12.0$ Hz, 1H), 1.71−1.67 (m, 3H), 1.51 (ddd, $J = 13.0, 12.5, 6.0$ Hz, 1H), 1.26 (t, $J = 7.5$ Hz, 3H), 0.18 (s, 9H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 102.8, 100.3, 90.6, 90.0, 83.3, 74.8, 61.0, 60.9, 43.1, 34.4, 31.1, 19.8, 14.0, 13.2, −0.3 (3 × C), −0.4 (3 × C); HRMS calcd for $C_{21}H_{33}IO_3Si_2$ M^+ 516.1013, found 516.1026. Anal. Calcd for $C_{21}H_{33}IO_3Si_2$: C, 48.83; H, 6.44. Found: C, 48.83; H, 6.29.

Compound **30,** colorless foam: R_f 0.70 (hexanes−ethyl acetate, 19:1, v/v); IR (neat) 2173, 1738, 1447, 1304, 1251, 845, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.19 (brd, $J = 4.8$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.00−2.90 (m, 1H), 2.79 (d, $J = 12.6$ Hz, 1H), 2.50 (d, $J = 12.6$ Hz, 1H), 2.02 (brdd, $J = 14.0, 7.5$ Hz, 1H), 2.04−1.94 (m, 2H), 1.50 (s, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 0.17 (s, 9H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 102.8, 99.7, 91.1, 89.8, 85.2, 75.1, 61.1, 60.4, 40.6, 35.6, 32.2, 27.2, 25.8, 14.0, −0.4 (3 × C), −0.5 (3 × C); HRMS calcd for $C_{21}H_{33}IO_3Si_2$ M^+ 516.1013, found 516.1003. Anal. Calcd for $C_{21}H_{33}IO_3Si_2$: C, 48.83; H, 6.44. Found: C, 48.69; H, 6.49.

(1*R,5*R**)-Ethyl 7,7-Diethynyl-5-iodomethyl-6-oxabicyclo-[3.2.1]octane-1-carboxylate (31) and (1*R**,5*R**)-7,7-Diethynyl-5-iodomethyl-6-oxabicyclo[3.2.1]-octane-1-carboxylic Acid (32).** A suspension of compound **29** (1.80 g, 3.49 mmol, 1.0 equiv) in a saturated aqueous solution of $Ba(OH)_2$ (100 mL) was stirred at 25 °C for 48 h. A 5% aqueous solution of HCl was added until the aqueous suspension was acid to pH paper. The reaction was extracted with CH_2Cl_2 (10 × 10 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 × mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography to yield compounds **31** (539 mg, 1.45 mmol, 41.5%) and **32** (661 mg, 1.92 mmol, 55%).

Compound **31** was isolated as a crystalline solid: mp 129−130 °C (*n*-hexane/CH_2Cl_2); R_f 0.30 (hexanes−ethyl acetate, 9:1, v/v); IR (KBr) 3292, 3267, 2117, 1717, 1300, 1048, 923, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.21 (dq, J = 9.7, 7.5 Hz, 1H), 4.17 (dq, J = 9.7, 7.2 Hz, 1H), 3.31 (d, J = 10.5 Hz, 1H), 3.29 (d, J = 10.5 Hz, 1H), 2.72 (ddd, J = 12.2, 2.2, 2.2 Hz, 1H), 2.69 (s, 1H), 2.60 (s, 1H), 2.37 (ddd, J = 13.3, 7.0, 2.3 Hz, 1H), 2.29−2.17 (m, 1H), 1.94 (d, J = 12.0 Hz, 1H), 1.78−1.67 (m, 3H), 1.65 (ddd, J = 13.3, 11.0, 6.0 Hz, 1H), 1.26 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 83.9, 81.7, 79.0, 74.4, 74.1, 73.8, 61.3, 60.0, 43.1, 34.3, 31.0, 19.7, 14.0, 12.6; HRMS calcd for $C_{15}H_{17}IO_3$ M^+ 372.0222, found 372.0218. Anal. Calcd for $C_{15}H_{17}IO_3$: C, 48.40; H, 4.60. Found: C, 48.42; H, 4.71.

Compound **32** was isolated as a crystalline solid: mp 130.8−131.5 °C (*n*-hexane/CH_2Cl_2); R_f 0.25 (hexanes−ethyl acetate, 1:1, v/v); IR (KBr) 3281, 2115, 1726, 1367, 1262, 1188, 1038, 921 cm^{-1}; ^1H NMR (MeOD, 300 MHz) δ 3.38 (d, J = 10.8 Hz, 1H), 3.29 (d, J = 10.8 Hz, 1H), 3.17 (s, 1H), 3.10 (s, 1H), 2.70 (d, J = 12.0 Hz, 1H), 2.39−2.33 (m, 1H), 2.28−2.23 (m, 1H), 1.91 (d, J = 12.0 Hz, 1H), 1.86−1.66 (m, 4H). Anal. Calcd for $C_{13}H_{13}IO_3$: C, 45.37; H, 3.81. Found: C, 45.35; H, 4.17.

(1*R,5*R**)-Ethyl 7,7-Diethynyl-5-hydroxymethyl-6-oxabicyclo-[3.2.1]octane-1-carboxylate (20).** A solution of compound **29** (100 mg, 0.19 mmol, 1.0 equiv) in dry DMSO (0.5 mL) was cannulated under Ar to a vigorously stirred mixture of powdered potassium superoxide (62 mg, 0.87 mmol, 4.5 equiv) and 18-crown-6-ether (23 mg, 0.087 mmol, 0.45 equiv) in dry DMSO (0.5 mL). The resulting mixture was stirred for 2.5 h at room temperature, at which time TLC showed no remaining **29**. The resultant orange solution was cautiously treated with a saturated aqueous solution of NaCl (1.0 mL). The solution was then diluted with ethyl acetate (3.0 mL) and washed with 3% aqueous HCl, H_2O, and saturated aqueous NaCl (2.0 mL each). The aqueous phases were further extracted with ethyl acetate (6 × 1.5 mL), and the combined organic phases dried over $MgSO_4$, filtered, and concentrated to give a yellow residue (38 mg), which was purified by silica gel column chromatography (hexanes−ethyl acetate, 1:1, v/v). Compound **20**-(R═Et) (5.0 mg, 0.02 mmol, 10%) was isolated as a crystalline solid: mp 113−114 °C (hexanes/CH_2Cl_2); R_f 0.38 (hexanes−ethyl acetate, 1:1; v/v); IR (KBr) 3230, 1710, 1460, 1366, 1317, 1267, 1052, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.19 (q, J = 7.1 Hz, 1H), 4.18 (q, J = 7.1 Hz, 1H), 3.59 (dd, J = 12.1, 3.4 Hz, 1H), 3.48 (dd, J = 12.1, 10.2 Hz, 1H), 2.95 (ddd, J = 12.1, 2.4, 2.4 Hz, 1H), 2.71 (s, 1H), 2.62 (s, 1H), 2.42 (ddd, J = 12.3, 7.0, 2.7 Hz, 1H), 2.21 (ddddd, J = 12.4, 12.4, 12.4, 6.6, 6.6 Hz, 1H), 1.90 (dd, J = 10.2, 3.4 Hz, 1H), 1.80−1.69 (m, 2H), 1.66 (d, J = 12.1 Hz, 1H), 1.64−1.59 (m, 1H), 1.32 (ddd, J = 12.0, 12.0, 5.8 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 86.6, 81.9, 78.8, 74.2, 73.8, 73.7, 65.4, 61.2, 60.2, 38.2, 31.7, 31.6, 19.1, 14.0; HRMS calcd for $C_{15}H_{18}O_4$ M^+ 262.1205, found 262.1191. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.50; H, 7.03.

X-ray Crystallography. Crystals of all compounds were grown under identical conditions using a previously water-saturated mixture of carbon tetrachloride/*n*-hexane as solvent. Crystal data were collected using a Nonius Kappa CCD diffractometer (λ(Mo Kα) = 0.7107 Å). Data for compounds **6**, **7**, and **21** were collected at 170 K while for the remaining compounds (**32**, **39**, **43**, **47**, and **48**) were collected at room temperature. Data reduction and cell refinement was carried out with the programs DENZO[34] and COLLECT.[35] Crystals of **7** and the anhydrous form of **1**(R_1═CH_2-OH, R_2═C_2H_5) are isomorphous. The unit cell volume in **7** is slightly greater than that in **1**(R_1═CH_2OH, R_2═C_2H_5), and the ethyl and vinyl substituents are disordered. Semiempirical absorption corrections in **32** and **39** were performed.[36] The structures were solved by direct methods,[37] and the refinement process has been carried on F^2 against all data using SHELX97.[38] All hydrogen atoms were located on difference Fourier maps and were allowed to ride during the last cycles of refinement. Details crystal data and geometrical parameters are deposited in the Supporting Information (CIF files).

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Supporting Information Available: Experimental procedures and spectroscopic data for all other compounds and ^1H and ^{13}C NMR spectra for all new compounds; CIF files containing detailed crystal data of compounds **6**, **7**, **21**, **32**, **39**, **43**, **47**, and **48**. This material is available free of charge via the Internet at http://pubs.acs.org.

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