JOC Article

Chromium(0)-Promoted Multicomponent Cycloaddition of Tethered Diynes with Cyclic Trienes: Application to the Total Synthesis of 9-*epi*-Pentalenic Acid

James H. Rigby,* Mundruppady S. Laxmisha, Andrew R. Hudson, Charles H. Heap, and Mary Jane Heeg

Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489

jhr@chem.wayne.edu

Received May 27, 2004

An efficient protecting group controlled regioselective chromium(0)-mediated three-component higher order cycloaddition of tethered diynes with cyclic trienes that generates five rings and six stereogenic centers in one step is described. Following a sequence of reactions featuring a chemoselective Baeyer−Villiger rearrangement and a regioselective cyclopropane hydrogenolysis, the total synthesis of 9-*epi*-pentalenic acid was achieved.

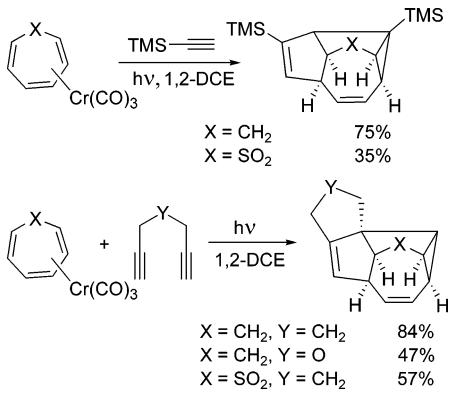
Introduction

In recent years, higher order cycloaddition has emerged as a powerful tool for the rapid assembly of stereochemically rich and structurally elaborate polycyclic systems.[1] Metal mediation of the cycloaddition process has resulted in advances in which ring constructions not normally accessible via conventional metal-free conditions have become almost routine. These metal-mediated cycloadditions have made possible efficient construction of a range of medium-sized-ring systems.[2]

Chromium(0)-promoted higher order cycloadditions, such as [6π+2π] and [6π+4π] combinations, have also received considerable attention in recent years due to their stereocomplementarity and periselectivity advantages over the corresponding metal-free cycloaddition processes.[3] An intriguing and potentially significant extension of this chromium(0)-mediated ring assembly has been realized with the recent discovery of a novel and efficient three-component, one-pot cycloaddition process, characterized by the Cr(0)-mediated combination of 2 equiv of an alkyne with a cyclic triene[4] to afford an unusual tetracyclic ring system (Scheme 1). An intramolecular variant of this reaction was also brought to practice in which the two reacting alkyne partners are tethered by spacers of various lengths and compositions.[5] Noteworthy features of this protocol include *simultaneous formation* of five rings and six stereogenic centers with excellent stereo- and regiocontrol.

While these sequences are quite attractive and show much promise in relatively simple applications, several important issues must be addressed in more complex situations if this methodology is to become synthetically useful. Among the most important of these is establishing a regioselectivity profile of the cycloaddition step when unsymmetrical diynes are employed. We now wish to report that this issue has been addressed in some detail in the context of the total synthesis of 9-*epi*-pentalenic acid, in which a chromium(0)-mediated three-component cycloaddition serves as the key strategy level transformation.

SCHEME 1. Chromium(0)-Mediated Multicomponent Cycloaddition



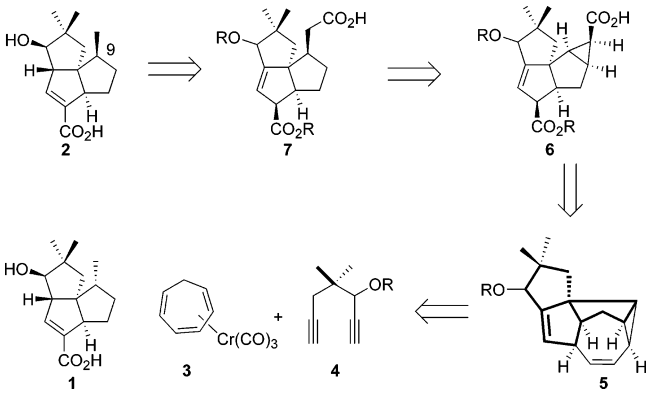
Pentalenic acid (**1**) was first isolated in 1978 from the fermentation broth of *Streptomyces griseochromogens*[6] and is believed to be the biogenetic precursor of the antibiotic pentalenolactone. There has been a sustained interest in the synthesis of pentalenic acid and several new approaches have been reported.[7] Initial inspection of our target molecule revealed, however, that while the current methodology would set all of the necessary stereocenters for the molecule in the cycloaddition event, one of the centers, at C-9, would be set in the opposite fashion to that present in the natural product. Consequently, we embarked on the synthesis of 9-*epi*-pentalenic acid (**2**). While 9-*epi*-pentalenic acid is not a natural product, and it has been synthesized previously,[7i] it would

(1) For general reviews on metal-catalyzed cycloadditions, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. (b) Hegedus, L. S. *Coord. Chem. Rev.* **1997**, *161*, 129−255. (c) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523−596. (d) Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27−76. (e) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662. (f) Hartley, R. C.; Caldwell, S. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 477−501. (g) Wender, P. A. *Pure Appl. Chem.* **2002**, *74*, 25−31.

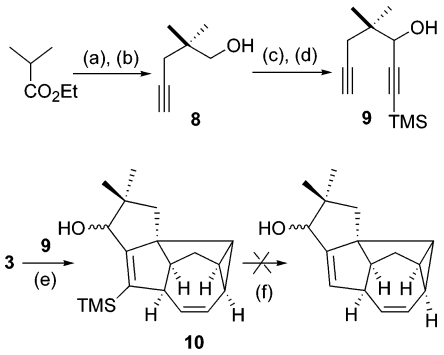
10.1021/jo040204o CCC: $27.50
Published on Web 09/03/2004

still represent an appropriate demonstration of our methodology. The salient features of our synthetic strategy are shown in Scheme 2. In terms of the synthesis end game, it was envisioned that the carboxylic acid **7**, derived from the cyclopropane carboxylic acid **6** by a regioselective cleavage of the sterically less encumbered cyclopropane bond, could be processed to deliver the target compound **2** by simple functional group transformations. The carboxylic acid **6** was seen to be available from the cycloadduct **5** by a regioselective oxidative cleavage of the less substituted double bond. At the outset of our investigation, crucial questions remained regarding the regiocontrol in the cycloaddition of unsymmetrical tethered diyne **4** and cycloheptatriene complex **3**, and a viable method to oxidatively cleave the less substituted double bond in **5**, to give two chemically distinguishable carbonyl functionalities as required in **6** for further chemical transformations. The notable features of this synthetic plan are the following: (a) it is fundamentally different from existing approaches to angular triquinane natural products, (b) all stereocenters present in the target are set in the initial cycloaddition reaction, leaving only functional group manipulations, and (c) only one carbon must be excised from the cycloadduct **5** to provide the target compound, thus making the synthesis very atom economical.[8]

SCHEME 2. Retrosynthesis of 9-*epi*-Pentalenic Acid



SCHEME 3. Multicomponent Cycloaddition of 9 with 3[a]



[a] Reagents and conditions: (a) LDA/propargyl bromide, THF, 94%; (b) LAH, ether, 90%; (c) DMSO, oxalyl chloride, Et_3N, CH_2Cl_2, 92%; (d) TMS-acetylene, *n*-BuLi, THF, 92%; (e) *hν* (Pyrex), 1,2-dichloroethane, 65 °C, 16%; (f) PTSA, $CH_3CN/THF/H_2O$ or Bu_4NCl, AcOH, CH_3CN.

Results and Discussion

As our synthetic plan required the use of an unsymmetrical diyne in the cycloaddition event, we first sought to investigate methods for controlling the regiochemistry of the diyne cycloaddition. The first approach was to block one end of the diyne with a trimethylsilyl group. The diyne **9**, which was prepared in four steps from ethyl isobutyrate (Scheme 3), was chosen initially to study this three-component cycloaddition.[9] Thus, alkylation of ethyl isobutyrate with LDA/propargyl bromide followed by lithium aluminum hydride reduction of the resulting ester gave alcohol **8**. Swern oxidation and subsequent

(2) For general reviews on metal-promoted medium-size-ring synthesis, see: (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3008. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930. (c) Sieburth, S. McN.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251−6282. Seven-membered-ring synthesis: (d) Trost, B. M.; Shen, H. C.; Schulz, T.; Koradin, C.; Schirok, H. *Org. Lett.* **2003**, *5*, 4149−4151. (e) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721. (f) Wender, P. A.; Pedersen, T. M.; Scanio, M. J. C. *J. Am. Chem. Soc.* **2002**, *124*, 15154−15155. (g) Trost, B. M.; MacPherson, D. T. *J. Am. Chem. Soc*, **1987**, *109*, 3483−3484. (h) Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61−66. (i) Hoffmann, H. M. R. *Angew Chem., Int. Ed. Engl.* **1984**, *23*, 1−19. (j) Schwiebert, K. E.; Stryker, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 8275−8276. Eight-membered-ring synthesis: (k) Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, *124*, 8782−8783. (*l*) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suárez-Sobrino, A.; Vågberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem*, **1997**, *62*, 4908−4909. (m) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815−7816. (n) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876−2877. (o) Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784−8785. (p) Brenner, W.; Heimbach, P.; Hey, H.; Müller, E. W.; Wilke, G. *Justus Liebigs Ann. Chem.* **1969**, *727*, 161. (q) Diercks, R.; Stamp, L.; tom Dieck, H. *Chem. Ber.* **1984**, *117*, 1913−1919. (r) Davis, R. E.; Dodds, T. A.; Hseu, T.-H.; Wagnon, J. C.; Devon, T.; Tancrede, J.; McKennis, J. S.; Pettit, R. *J. Am. Chem. Soc.* **1974**, *96*, 7562−7564. (s) Lautens, M.; Tam, W.; Sood, C. *J. Org. Chem.* **1993**, *58*, 4513−4515. (t) Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Henshilwood, J. A.; Short, K. M.; Sugathapala, P. M. *Tetrahedron* **1993**, *49*, 5495−5506. Nine-membered ring: (u) Kreiter, C. G.; Lehr, K.; Leyendecker, M.; Scheldrick, W. S.; Exner, R. *Chem. Ber.* **1991**, *124*, 3−12. (v) Kreiter, C. G.; Lehr, K. *J. Organomet. Chem.* **1993**, *454*, 199−204. Ten-membered ring: (w) Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 1382−1396.

(3) (a) Rigby, J. H. *Tetrahedron* **1999**, *55*, 4521−4538. (b) Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579−585. (c) Chaffee, K.; Huo, P.; Sheridan, J. B.; Barbieri, A.; Aistars, A.; Lalancette, R. A.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 1900−1907. (d) Chaffee, K.; Sheridan, J. B.; Aistars, A. *Organometallics* **1992**, *11*, 18−19. (e) Özkar, S.; Kurz, H.; Neugebauer, D.; Kreiter, C. G. *J. Organomet. Chem.* **1978**, *160*, 115−124.

(4) (a) Rigby, J. H.; Warshakoon, N. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6094−6095. (b) Chen, W.; Chaffee, K.; Chung, H.-J.; Sheridan, J. B. *J. Am. Chem. Soc.* **1996**, *118*, 9980−9981.

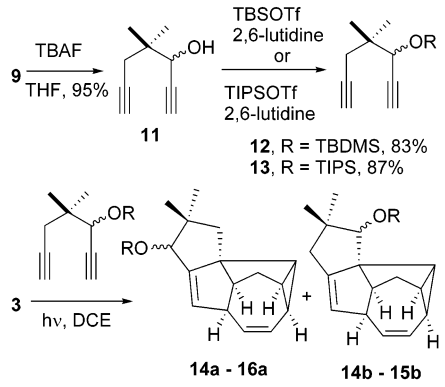
(5) Rigby, J. H.; Heap, C. R.; Warshakoon, N. C. *Tetrahedron* **2000**, *56*, 2305−2311.

(6) Seto, H.; Sasaki, T.; Uzawa, J.; Takeuchi, S.; Yonehara, H. *Tetrahedron Lett.* **1978**, *19*, 4411−4412.

(7) For excellent reviews of approaches to triquinane ring systems and related natural products, see: (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671−720. (b) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41−165. (c) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1−158. For previous syntheses of pentalenic acid, see: (d) Crimmins, M. T.; DeLoach, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 800−806. (e) Crimmins, M. T.; DeLoach, J. A. *J. Org. Chem.* **1984**, *49*, 2076−2077. (f) Sakai, K.; Ohtsuka, T.; Misumi, S. *Chem. Lett.* **1981**, 355−358. (g) Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 7424−7426. (h) Ihara, M.; Katogi, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2963−2970. (i) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G.; Ranu, B. C.; Papadopolous, P. *Tetrahedron* **1987**, *43*, 5685−5721. For previous approaches to pentalenic acid, see: (j) Bintz-Giudicelli, C.; Weymann, O.; Uguen, D. *Tetrahedron Lett.* **1997**, *38*, 2841−2844. (k) Rowley, E. G.; Schore, N. E. *J. Org. Chem.* **1992**, *57*, 6853−6861. (*l*) Seo, J.; Fain, H.; Blanc, J.-B.; Montgomery, J. *J. Org. Chem.* **1999**, *64*, 6060−6065.

(8) Trost, B. M. *Science* **1991**, *254*, 1471−1484.

SCHEME 4. Regiocontrol in the Higher Order Cycloaddition of O-Silylated Diynes



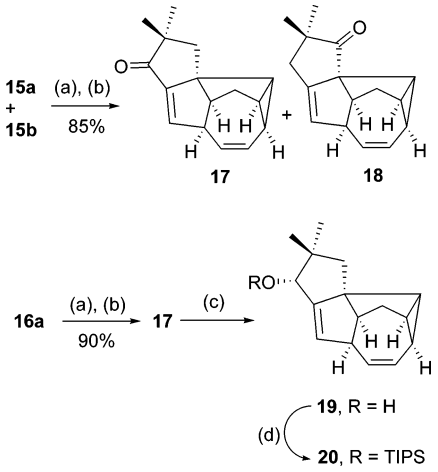
TMS-acetylide addition afforded **9**, required for the cycloaddition. The cycloaddition of **9** with complex **3** worked well in terms of dictating the regiochemistry of the cycloaddition to give the cycloadduct **10** as a single regioisomer, but the yield of the reaction was very poor, most likely due to a very slow rate of the second intramolecular homo[6+2] reaction, which allows more time for other side reactions such as decomplexation to occur. Another problem with employing the TMS blocking approach in a synthetic effort is the eventual removal of the vinylic silyl group at some point. This is not always a trivial proposition as evidenced by two unsuccessful attempts to cleave the TMS group in **10** with PTSA in $CH_3CN/THF/H_2O$ at 65 °C[10] or Bu_4NCl and AcOH in CH_3CN,[11] both of which resulted in virtually complete recovery of starting material.

The second approach to control the regiochemistry of the cycloaddition was to increase the steric bulk in the vicinity of one of the alkynes. Toward this end, cycloadditions were performed with a series of diynes having protecting groups of different steric bulk on the propargylic hydroxyl group (Scheme 4). While the cycloaddition of the diyne **11** having a free hydroxyl group with complex **3** gave a mixture of regioisomeric cycloadducts in poor yield, better results were obtained when TBS protected diyne **12** was employed. This reaction gave the corresponding cycloadducts in 65% overall yield and 14:1 regioselectivity in favor of the required regioisomer **15a**. The best result in terms of regioselectivity and reaction yield was obtained when the sterically more demanding TIPS group was used as the protecting group. Thus, photolysis of complex **3** in 1,2-dichloroethane with slow addition of diyne **13** gave the desired cycloadduct **16a** in 70% yield as the sole observable regioisomer.[12] The cycloadducts in these examples were obtained as a 1:1 mixture of diastereoisomers at the oxygen-substituted position.The ratio of regioisomers was determined by

TABLE 1. Evaluation of Regioselectivity in the Chromium(0)-Mediated Three-Component Cycloaddition

entry	R	products	ratio (**a**:**b**)	yield, %
1	H	**14a** and **14b**	1.8:1	36
2	TBS	**15a** and **15b**	14:1	65
3	TIPS	**16a**	100:0	70

SCHEME 5. Determination of the Ratio of Regioisomers[a]



[a] Reagents and conditions: (a) TBAF, THF; (b) TPAP, NMO, CH_2Cl_2; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C, 87%; (d) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 93%.

conversion of the alcohols into the corresponding ketones by cleavage of the protecting groups (if necessary) and oxidation with TPAP/NMO (Scheme 5).[13] The oxidation removed the problem of dealing with four stereoisomers in the mixture of cycloadducts and formation of α,β-unsaturated ketone **17** with an olefinic proton at δ 6.56 allowed for facile differentiation of the two regioisomers. Enone **17** was reduced under Luche conditions[14] at −78 °C to give the allylic alcohol **19** as a single diastereoisomer. Although this avoided the problem of dealing with a mixture of diastereoisomers for the rest of the synthetic sequence, X-ray analysis of the product showed that the hydroxyl group stereochemistry was opposite to that present in the target. Attempts to reduce the enone **17** with DIBAL and LAH afforded predominantly the 1,4-reduced products, while efforts to invert the alcohol stereochemistry in **19** by Mitsunobu and modified Mitsunobu conditions[15] led to the recovery of starting material. It was assumed that the hydroxyl group stereochemistry could be set by an oxidation−reduction protocol at a later stage and the synthesis was advanced from alcohol **19**. This decision was predicated on the fact that in some of the previous syntheses of pentalenic acid, the hydroxyl group stereochemistry at C-1 was set by a dissolving metal reduction of the corresponding ketone late in the synthesis.[7d,h] The alcohol **19** was protected as its TIPS ether by treatment with TIPSOTf and 2,6-lutidine in dichloromethane to give **20** as a single diastereoisomer.

(9) (a) Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483−1486. (b) Ojima, I.; Kass, D. F.; Zhu, J. *Organometallics* **1996**, *15*, 5191−5195. (c) Pearson, A. J.; Shively, Jr, R. J. *Organometallics* **1994**, *13*, 578−584. (d) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Kawaguchi, H.; Tatsumi, K.; Itoh, K. *J. Am. Chem. Soc.* **2000**, *122*, 4310−4319.

(10) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824−825.

(11) Kojima, A.; Takemoto, T.; Sodeoka, M.; Shibasaki, M. *Synthesis* **1998**, 581−589.

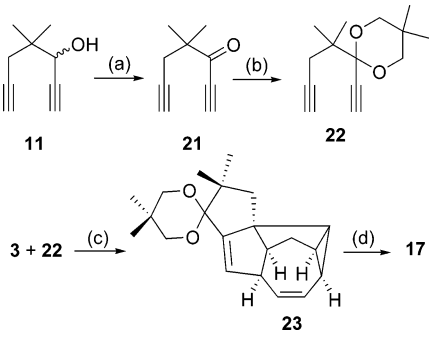
(12) Although electronic factors cannot be ruled out in dictating the regioselectivity of the cycloaddition, marked improvement in the regioselectivity observed when an electronically similar TBS group was replaced by a TIPS group indicates that steric effects are predominant.

(13) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

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

(15) (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380−2382. (b) Mukaiyama, T.; Shintou, T.; Fukumoto, K. *J. Am. Chem. Soc.* **2003**, *125*, 10538−10539.

SCHEME 6. Higher Order Cycloaddition of 22[a]



[a] Reagents and conditions: (a) CrO_3, H_2SO_4, H_2O, 86%; (b) 2,2-dimethylpropane-1,3-diol, PTSA, benzene, 48%; (c) *hν*, DCE, 45%; (d) PTS, acetone, 29%.

One limitation of this cycloaddition methodology is the lack of control at the newly formed alcohol stereocenter in the cycloadduct **16a**. However, since the cycloaddition affords such a large increase in molecular complexity in a single chemical operation, it was considered acceptable. A potential solution to this problem would be to use a diyne that possesses a hydroxyl group surrogate, which does not generate a new stereocenter during the cycloaddition step. The diyne **22** was viewed as an ideal choice for this purpose. The requisite diyne **22** was prepared from **11** by an oxidation and protection protocol through the intermediate ynone **21** as shown in Scheme 6. Cycloaddition of **22** with **3** gave the adduct **23** as a single regioisomer, albeit in moderate yield. It was known from earlier work that the enone **17** could be selectively reduced to give alcohol **19** in good yields. Therefore the deprotection of the acetal moiety in **23** was attempted under acidic conditions. This seemingly simple transformation, however, proved difficult and the best yield (29%) for the deprotection was obtained when PTSA in acetone was used. At this point, it was deemed prudent to proceed with the projected synthesis with use of pentacycle **20**.

Regioselective Cleavage of the Disubstituted Alkene. With diene **20** in hand, work was initiated toward the regioselective oxidative cleavage of the disubstituted alkene moiety in the presence of the ostensibly more reactive trisubstituted olefin. As mentioned before, the completion of the synthesis relies not only on successful regioselective oxidative cleavage of the disubstituted olefin, but also on a viable method for successfully differentiating the two resulting carbonyl groups. After many unsuccessful attempts to regioselectively epoxidize the disubstituted double bond,[16] osmium tetroxide catalyzed dihydroxylation was investigated. This reaction, however, proved to be troublesome and required a detailed investigation. The UpJohn dihydroxylation conditions[17] resulted in mostly recovered starting material, as did dihydroxylation under stoichiometric conditions in conjunction with TMEDA.[18] After some experimentation, the dihydroxylation was achieved with moderate regioselectivity with use of OsO_4 (20 mol %), potassium ferricyanide as the co-oxidant, a large excess of hydrolysis aid ($MeSO_2NH_2$), and pyridine (1 equiv).[19] Under these conditions the desired diol **24** was obtained as the major product in 51% yield along with regioisomeric diol **25** and tetraol **26**. The reaction was amenable to scale-up giving sufficient quantities of **24** for further use. Efforts were made to improve the regioselectivity of the dihydroxylation by using a bulky ligand[20] on osmium, which gave the undesired diol **25** as the major product.With diol **24** in hand, we began to explore the most effective means of cleavage to gain access into the angular triquinane skeleton. Due to the problems encountered in simpler systems with the oxidative cleavage of the diol and being cognizant of the need to differentiate the resultant carbonyl groups, alternative routes to achieve these objectives were pursued. Among the more attractive options was a sequence involving a Baeyer−Villiger rearrangement of the vicinal diketone **27**.[21] It was believed that the differentiation of the two carbonyl groups could be achieved by careful opening of the anhydride **28** with an alkoxide or alcohol nucleophile to yield the corresponding ester **29**. Although examination of molecular models did not give a clear indication as to which of the two carbonyl groups in **28** would be more accessible, it was assumed that the presence of a cyclopropyl group adjacent to one of them would assist in the proper regiochemical outcome.

The diol **24** was oxidized with DMSO/trifluoroacetic anhydride to give the vicinal dione **27** in good yield.[22] Treatment of **27** with *m*-CPBA (1.3 equiv) at 0 °C, buffered with an excess of $NaHCO_3$, gave the cyclic anhydride **28** in excellent yield[23] and no trace of epoxide formation was observed. Although Baeyer−Villiger rearrangement of cyclic vicinal diones to corresponding anhydrides has been reported,[23e−f,24] to the best of our knowledge, the formation of eight-membered anhydrides by the Baeyer−Villiger reaction of cyclic seven-membered vicinal diones is without precedent in the literature. This outcome is all the more significant because it left a potentially reactive olefin untouched during the reaction.[24] With cyclic anhydride **28** in hand, the ring opening proved straightforward. As anticipated on electronic grounds, treatment of **28** with methanol and triethylamine in CH_2Cl_2 gave ester **29** as a single regioisomer.

Regioselective Cleavage of the Cyclopropane Ring. With a viable strategy for the synthesis of the tricyclic core at our disposal, the next task in the

(16) Epoxidation attempts with *m*-CPBA gave a complex mixture of products.

(17) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976.

(18) Tomioka, K. *Synthesis* **1990**, 541−549.

(19) Johnson, R. A,; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.

(20) Andrus, M. B.; Lepore, S. D.; Sclafani, J. A. *Tetrahedron Lett.* **1997**, *38*, 4043−4046.

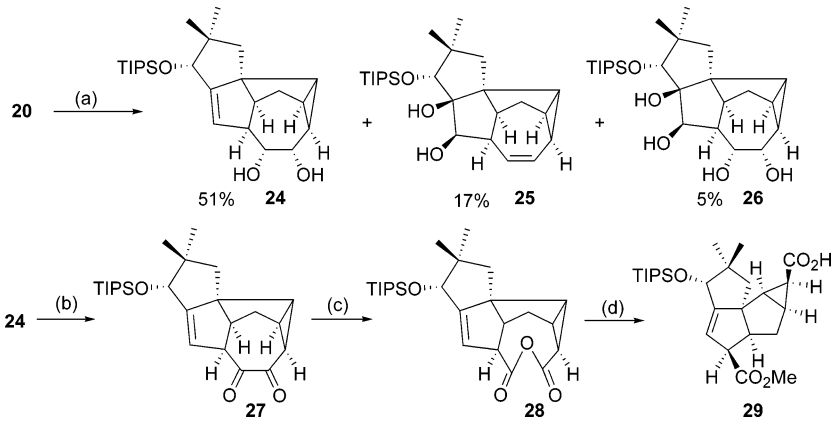
(21) Mechanistically, this rearrangement is slightly different from the normal Baeyer−Villiger rearrangement of ketones when *m*-CPBA is used. For details, see: Cullis, P. M.; Arnold, J. R. P.; Clarke, M.; Howell, R.; DeMira, M.; Naylor, M.; Nicholls, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1088−1089.

(22) Amon, C. M.; Banwell, M. G.; Gravatt, G. L. *J. Org. Chem.* **1987**, *52*, 4851−4855.

(23) For some examples of Baeyer−Villiger rearrangement of vicinal diones to anhydrides, see: (a) Kwart, H.; Wegemer, N. J. *J. Am. Chem. Soc.* **1961**, *83*, 2746−2755. (b) Sawaki, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 6292−6296. (c) Leffler, J. E. *J. Org. Chem.* **1951**, *16*, 1785−1787. (d) Hassall, C. H. *Org. React.* **1957**, *9*, 73. (e) Jacobs, R. T.; Feutrill, G. I.; Meinwald, J. *J. Org. Chem.* **1990**, *55*, 4051−4062. (f) Komarov, I. V.; Monsees, A.; Kadyrov, R.; Fischer, C.; Schmidt, U.; Börner, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1615−1620.

(24) A Baeyer−Villiger rearrangement of medium-size cyclic 1,2-diones in the presence of an olefin has been reported but the chemoselectivity was very poor, see: Mayer, W.; Meier, H. *Chem. Ber.* **1989**, *122*, 509−517.

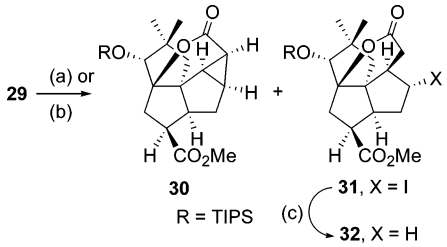
SCHEME 7. Regioselective Dihydroxylation and Anhydride Opening[a]



[a] Reagents and conditions: (a) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, py, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1); (b) DMSO, $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 93%; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 96%; (d) MeOH, Et_3N, CH_2Cl_2, 89%.

synthetic sequence was the regioselective cleavage of the cyclopropane moiety in acid **29**. Unfortunately, this projected cleavage was found to be particularly difficult under a variety of conditions. For example, catalytic hydrogenation-based methods led to recovery of starting material while dissolving metal reduction attacked the ester group to give the corresponding alcohol, while leaving the cyclopropane unit intact. We next investigated trimethylsilyl iodide-mediated cyclopropyl ring cleavage. Although there have been a number of reports on TMSI-mediated cleavage of cyclopropyl ketones[25] and cyclopropyl carboxylic esters,[26] we could identify only one report of cyclopropyl carboxylic acid cleavage with TMSI.[27] Attempted opening of the cyclopropane ring in **29** under the reported conditions appeared to result in no reaction after several hours at ambient temperature. However, much to our surprise, lactone **30** was isolated as the major product along with recovered acid after aqueous workup of the reaction. The likely mechanism for this process involves a cationic cyclization of the acid mediated by the putative acid generated upon addition of water. Indeed, treatment of acid **29** with hydriodic acid (1.1 equiv) in CH_2Cl_2 for less than 2 h gave lactone **30** in a respectable 82% yield. This reaction also gave a minor product, the structure of which was established by X-ray analysis as the iodolactone **31**. It was assumed that iodolactone **31** presumably arises by a tandem acid-catalyzed lactonization and regioselective iodide-mediated cyclopropane cleavage.[28] Initial experiments to drive this process toward **31** revealed that the cyclopropane cleavage was extremely sluggish and required longer reaction times. However, the reaction rate can be increased by using excess HI at the expense of the overall reaction yield. The optimum result was obtained by stirring **29** for 24 h with HI (3 equiv) in CH_2Cl_2, which gave the iodide **31** and the lactone **30** in 40% and 19% yields, respectively. Reductive removal of the iodide in **31** with tributyltin hydride in refluxing toluene was straightforward, furnishing lactone **32** in 92% yield (Scheme 8).

SCHEME 8. One-Pot Lactonization and Cyclopropane Cleavage[a]



conditions	30	31
(a)	82%	15%
(b)	19%	40%

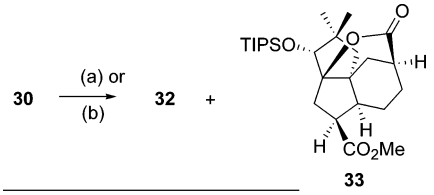
[a] Reagents and conditions: (a) HI (1.1 equiv), CH_2Cl_2, 2 h; (b) HI (3 equiv), CH_2Cl_2, 24 h; (c) *n*-Bu_3SnH, AIBN, toluene, reflux, 92%.

It was anticipated that this lactonization protocol would facilitate the synthesis of the target molecule. However, compound **30** could also present a selectivity issue between the two similar carbonyl groups. The need to invert the stereochemistry of the hydroxyl group at C-1 and to decarboxylate the acid derived from the lactone at some stage provided an ideal situation to deal with the lactone moiety at a later stage in the synthesis. Consequently, the immediate focus in the synthetic sequence was to find methods to improve the efficacy of the cyclopropane cleavage process. Although the regioselective cyclopropane cleavage was accomplished during the unanticipated acid-catalyzed lactonization of acid **29**, the yields were disappointing and an alternative method was sought.

Catalytic hydrogenation, which was unsuccessful with acid **29**, was now attempted on lactone **30**. After some experimentation, it was found that hydrogenolysis of **30** with Pearlman's catalyst[29] under a hydrogen atmosphere

(25) Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2412−2414.
(26) Brown, S. P.; Bal, B. S.; Pinnick, H. W. *Tetrahedron Lett.* **1981**, *22*, 4891−4894.
(27) Buttinelli, P.; Gargaro, G.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Gazz. Chim. Ital.* **1985**, *115* (3), 155.
(28) Treatment of the lactone **30** with HI indeed gave iodolactone **31** along with recovered starting material, which confirmed that **30** is an intermediate in this tandem lactonization and cyclopropane cleavage.
(29) Pearlman, W. M. *Tetrahedron Lett.* **1967**, *8*, 1663−1664.

SCHEME 9. Complementary Regioselectivity in Cyclopropane Hydrogenolysis[a]



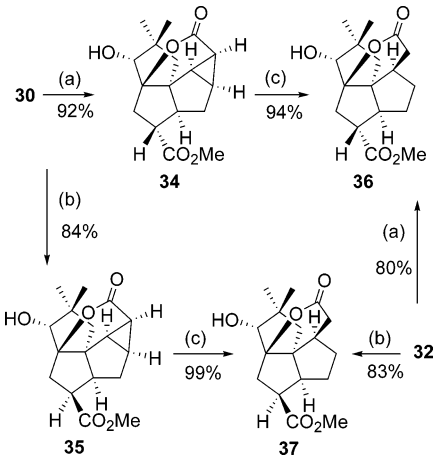
conditions	32	33
(a)	80%	14%
(b)	12%	72%

[a] Reagents and conditions: (a) H_2, $Pd(OH)_2$, EtOH, 5−7 days; (b) H_2, PtO_2, EtOAc, 56 h.

at atmospheric pressure gave the desired regioisomer **32** in 80% yield along with the undesired product **33** (14%) (Scheme 9). Due to poor solubility of the substrate in ethanol, which necessitated the use of high dilution conditions, the reaction was very sluggish requiring 5 to 7 days to reach completion.[30] In an effort to accelerate the reaction, hydrogenolysis of **30** was also carried out with Adam's catalyst. Although the reaction was much faster in this case, it led to a reversal in cleavage regioselectivity to give **32** and **33** in 12% and 72% yields, respectively. The structure of **33** was unambiguously established by X-ray analysis of the deprotected alcohol. Although we do not know the origin of this unusual selectivity, to the best of our knowledge the observed regioselectivity preference in the catalytic hydrogenation of bicyclo[3.1.0]hexanes is without precedent.[31] While the discovery of this unusual hydrogenation is of no significance to the current synthesis, potential synthetic applications of this reaction, in other contexts, are currently being examined in our group.

The successful regioselective cleavage of lactone **30** with Pearlman's catalyst prompted a more detailed investigation of this hydrogenation process in an effort to shorten the reaction time. As mentioned above, the real problem encountered in this reaction was the poor solubility of **30** in ethanol. It was reasoned that the cleavage of the TIPS protecting group in **30** before the cyclopropane hydrogenolysis would make the material more soluble and would thus accelerate this process. Toward this end, the deprotection of the TIPS group in **30** was attempted. Under standard deprotection conditions (TBAF/THF), the TIPS group in **30** was indeed cleaved to give the corresponding alcohol, but the reaction was accompanied by a competing epimerization of the ester group. The mixture of epimers proved difficult to separate and a better method to deprotect the TIPS group without any epimerization or with complete epimerization was sought. After a detailed investigation, it was found that the addition of 4 Å molecular sieves to the reaction mixture containing TBAF deprotected the TIPS ether in **30** to give **34** with complete epimerization at the

SCHEME 10. Improved Conditions for Cyclopropane Cleavage[a]



[a] Reagents and conditions: (a) TBAF, THF, 4 Å MS; (b) TBAF, THF/H_2O (3:1); (c) H_2, $Pd(OH)_2$ (30 mol %), EtOH, 48 h.

ester center, while addition of water served to deprotect the TIPS group to give **35** without any concomitant epimerization. The epimeric alcohols **34** and **35** were now very soluble in ethanol and the cyclopropane hydrogenolysis with $Pd(OH)_2$ was complete in 2 days, giving **36** and **37**, respectively, as single regioisomers in high yields. These conditions for cyclopropane cleavage are a significant improvement over the previous conditions for the hydrogenation of lactone **30,** which not only was sluggish, but also gave a mixture of regioisomers **32** and **33**. The alcohols **36** and **37** were found to be identical with those obtained by the deprotection of TIPS ether **32** under conditions identical with those described for the deprotection of **30** (Scheme 10).

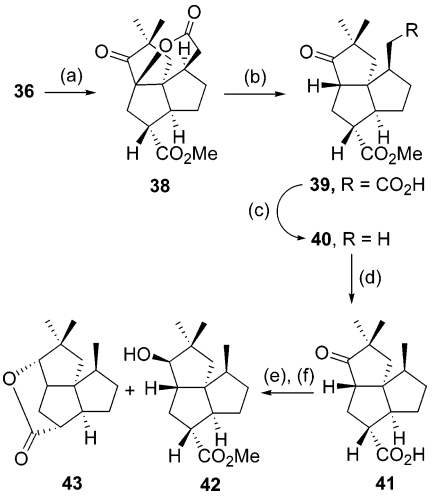
With a viable method for the regioselective cleavage of the cyclopropane in hand, the synthesis continued. The next focus became the opening of the lactone and decarboxylation of the resulting acid to reveal the methyl group present at C-9 in the target molecule. Significantly, this represents the only carbon atom present in the initial cycloadduct **16a** that does not appear in the final target molecule. It was presumed that a carbonyl group situated adjacent to the lactone would provide an appropriate handle to open this function by a ketyl radical-mediated process. The ketone was also necessary for the projected dissolving metal reduction to install the hydroxyl group with the requisite stereochemistry at C-1 of the target molecule. To implement this objective, alcohol **36** was oxidized with TPAP/NMO[13] to give the ketone **38** in good yield (Scheme 11). With **38** in hand, the critical ketyl radical-mediated opening of the lactone moiety was next investigated. The reagent of choice for this transformation was SmI_2. However, all attempts to open the lactone with SmI_2 led to recovery of starting material.[32] In contrast, treatment of lactone **38** with tributyltin hydride and catalytic AIBN in refluxing toluene furnished the desired acid **39**. Although tributyltin hydride has been used for the cleavage of acetates and benzoates situated adjacent to ketones,[33] to the best of our knowledge this represents the first example of tin hydride-mediated

(30) Use of other solvents such as ethyl acetate for the hydrogenation completely suppressed the reaction.

(31) A detailed study of hydrogenation of bicyclo[*n*.1.0]alkanes with Pt and Pd/C has been reported, see: Stahl, K.-J.; Hertzsch, W.; Musso, H. *Liebigs Ann. Chem*. **1985**, 1474. A similar regioselectivity preference in the opening of fused cyclopropanes has been observed with Zeise's dimer-catalyst, see: Ma, B.; Snyder, J. K. *Org. Lett*. **2002**, *4*, 2731−2734.

(32) Molander, G. A.; Hahn, G. *J. Org. Chem*. **1986**, *51*, 1135−1138.

SCHEME 11. Dissolving Metal Reduction of 41[a]



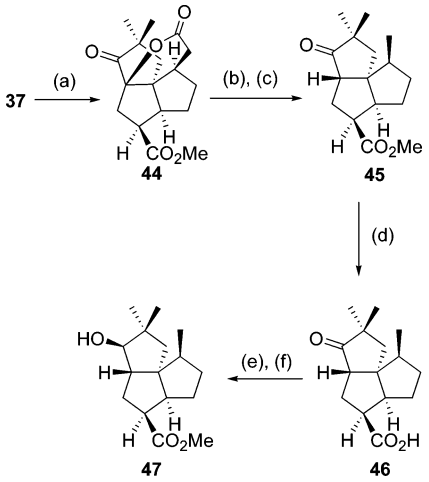
[a] Reagents and conditions: (a) TPAP, NMO, CH_2Cl_2, 84%; (b) *n*-Bu_3SnH, AIBN, toluene reflux; (c) 2,2′-di-thiopyridine-1,1′-di-*N*-oxide, PPh_3, then *t*-BuSH, irradiation with a 150-W tungsten lamp, 86%; (two steps); (d) KOH, MeOH, 90%; (e) NaH/THF, NH_3, MeOH, Li; (f) $TMSCHN_2$, MeOH (50% of **42** and 16% of **43**; over two steps).

opening of sterically hindered lactones. Due to the polarity of **39**, several attempts to separate the acid from the tin residues met with limited success and, consequently, purification was delayed until after the decarboxylation. Thus, after evaporation of the solvent and volatiles, a CH_2Cl_2 solution of the crude acid **39** was treated with 2,2′-dithiopyridine-1,1′-di-*N*-oxide and triphenylphosphine, followed by irradiation in the presence of *t*-BuSH to provide the decarboxylated product **40** in 86% yield over two steps.[34] The spectral data of the ester **40** were similar to the analogous compound reported in the natural series.[7h]

All that remained was to finish the synthesis of 9-*epi*-pentalenic acid by using the steps as reported previously for the C-9 epimer of **40** in the natural series.[7h] Thus, hydrolysis of the ester **40** with KOH/MeOH afforded acid **41**. Dissolving metal reduction of **41** with Li/NH_3 in the presence of MeOH as the proton source followed by esterification with $TMSCHN_2$ gave alcohol **42** in 50% yield along with lactone **43** in 16% yield, which arose from lactonization of the wrong diastereoisomer. This result was particularly surprising since dissolving metal reduction of the analogous ketone having the natural C-9 configuration reportedly gave a single diastereoisomer. Analysis of molecular models revealed no obvious interaction between the methyl group at C-9 and the carbonyl group.

Although dissolving metal reduction of **41** gave disappointing results compared to those of the related ketone in the natural series, this strongly suggested that subtle

SCHEME 12. Dissolving Metal Reduction of 46[a]



[a] Reagents and conditions: (a) TPAP, NMO, CH_2Cl_2, 93%; (b) *n*-Bu_3SnH, AIBN, toluene, reflux; (c) 2,2′-dithiopyridine-1,1′-di-*N*-oxide, PPh_3, then *t*-BuSH, irradiation with a 150-W tungsten lamp, 77% (two steps); (d) KOH, MeOH, 83%; (e) NaH/THF, NH_3, MeOH, Li; (f) $TMSCHN_2$, MeOH, 75% (two steps).

changes at remote positions in the substrate structure can have a significant effect on the diastereoselectivity of the process. This prompted us to investigate the dissolving metal reduction of the epimeric keto-acid **46**. The stereochemistry of the carboxylic group is inconsequential for the synthesis since a double bond is introduced in the next step. Efforts to epimerize ester **40** with NaOMe/MeOH led to an inseparable mixture of **40** and **45**. This result prompted an effort to prepare acid **46** having the epimeric carboxylic group from alcohol **37**. Following the same sequence of reactions as described for the conversion of **36** into **41**, carboxylic acid **46** was efficiently obtained from **37** in four steps (Scheme 12). Dissolving metal reduction of **46** followed by esterification with $TMSCHN_2$ furnished ester **47** in 75% yield as a single diastereoisomer, whose structure was unambiguously established by single-crystal X-ray analysis. This revealed that the stereochemistry of all relevant stereocenters in **47** was correct as required in the target molecule.

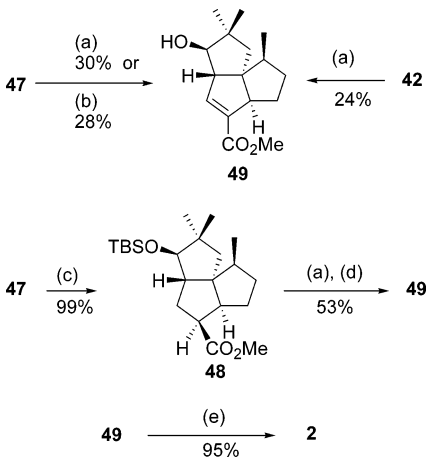
With **42** and **47** in hand, the final stage in the synthesis of the target molecule required the installation of a double bond adjacent to the ester group. This transformation was expected to be straightforward with use of selenium chemistry. However, as pointed out previously, both compounds **42** and **47** are epimeric to the natural series at C-9, and as it turned out, this minor difference contributed significantly to the difficulties faced in trying to introduce the requisite double bond. Thus, reaction of **42** and **47** with LDA/PhSeCl followed by selenoxide elimination with H_2O_2/AcOH gave **49** in 24% and 30% yield, respectively (Scheme 13). Similar results were obtained when this transformation was carried out with Trost's sulfenylation chemistry, which gave **49** in 28% yield.[35] A number of other conditions, such as α-halogenation, were attempted but to no avail. Owing to the difficulties faced in this transformation presumably due

(33) Redlich, H.; Neumann, H.-J.; Paulsen, H. *Chem. Ber.* **1977**, *110*, 2911−2921. For the tributyltin hydride-mediated cleavage of tertiary α-acetoxy carbonyl compounds, see: Grewal, R. S.; Hayes, P. C.; Sawyer, J. F.; Yates, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1290−1292. For the cleavage of benzoates, see: Chen, S.-H.; Wei, J.-M.; Vyas, D. M.; Doyle, T. W.; Farina, V. *Tetrahedron Lett.* **1993**, *34*, 6845−6848.

(34) (a) Barton, D. H. R.; Samadi, M. *Tetrahedron* **1992**, *48*, 7083−7090. (b) Anaya, J.; Barton, D. H. R.; Caballero, M. C.; Gero, S. D.; Grande, M.; Laso, N. M.; Hernando, J. I. M. *Tetrahedron: Asymmetry* **1994**, *5*, 2137−2140.

(35) (a) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363−382. (b) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887−4902.

SCHEME 13. Synthesis of 9-*epi*-Pentalenic Acid[a]



[a] Reagents and conditions: (a) (i) LDA, THF, PhSeCl, (ii) H_2O_2, AcOH, THF, 0 °C; (b) (i) LDA, THF, $PhSSO_2Ph$, (ii) *m*-CPBA (1 equiv), CH_2Cl_2, 0 °C; (iii) toluene reflux; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) TBAF, THF; (e) 10% aq KOH, MeOH, 55 °C.

to the free hydroxyl group in **47**, this hydroxyl group was protected by treatment with TBSOTf and 2,6-lutidine to give TBS ether **48**. Treatment of **48** with LDA/PhSeCl followed by selenoxide elimination and deprotection gave the unsaturated ester **49** in a respectable 53% yield. Finally, hydrolysis of **49**, following literature conditions,[7h] gave 9-*epi*-pentalenic acid (**2**).

Compounds **49** and **2** exhibited spectral data fully consistent with the assigned structures. In view of the lack of conclusive literature data for comparison,[36] further support for the structure of **49** came from the reduction of **49** with Mg/MeOH,[37] which gave an epimeric mixture of **42** and **47**.

Conclusions

Through the total synthesis of 9-*epi*-pentalenic acid, we have illustrated the utility and demonstrated several critical aspects of the Cr(0)-mediated higher order cycloaddition. Several novel and interesting regio- and chemoselective processes were developed during the course of the study. In addition, an unanticipated one-pot lactonization and cyclopropane cleavage has been observed during the synthesis. One lesson learned from this study is that minor structural variations at remote centers, particularly in the angular triquinane skeleton, can unexpectedly alter the efficiency and diastereoselectivity of otherwise routine chemical transformations.

Experimental Section

Diene 16a. A vigorous stream of argon was bubbled through 1,2-dichloroethane (1.5 L) in a photochemical reactor (outfitted with a water-cooled Pyrex filter) for 0.5 h. Tricarbonylcycloheptatriene chromium(0) complex (2.0 g, 8.8 mmol) was added and a vigorous stream of argon was bubbled through the red solution for a further 0.5 h. The solution was irradiated with a medium-pressure mercury light under a steady flow of argon as a solution of diyne **13** (2.32 g, 8.79 mol) in 1,2-dichloroethane (10 mL) [placed outside the photochemical box] was added dropwise to the photochemical reactor via syringe pump over a 2-h period. After the addition was complete the lamp was switched off and the green solution was concentrated under reduced pressure. The residue was taken up in 1:1 hexanes: dichloromethane (500 mL), filtered through a pad of Celite, and washed with dichloromethane (100 mL) and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (hexanes) yielded diene **16a** as a 1:1 mixture of diastereomers (2.5 g, 70%), which were separated after intensive purification. Data for the more polar diastereoisomer: R_f 0.7 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (dd, J = 12.0, 6.8 Hz, 1H), 5.56 (ddd, J = 11.2, 7.6, 1.6 Hz, 1H), 5.52 (t, J = 2.8 Hz, 1H), 4.42 (d, J = 2.4 Hz, 1H), 2.77 (td, J = 7.2, 3.2 Hz, 1H), 2.59 (t, J = 8.8 Hz, 1H), 1.91 (ddd, J = 13.6, 8.8, 4.8 Hz, 1H), 1.72 (td, J = 7.6 Hz, 4.8, 1H), 1.61 (d, J = 13.8 Hz, 1H), 1.57 (d, J = 13.8 Hz, 1H), 1.47 (d, J = 12.8 Hz, 1H), 1.25−1.20 (m, 2H), 1.13−1.03 (m, 24H), and 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 131.6, 125.3, 124.6, 80.3, 60.6, 59.7, 49.5, 48.7, 43.2, 33.0, 29.0, 28.9, 26.5, 23.0, 22.5, 18.5, 18.4, 12.9; IR (neat) 3020, 2946, 2927, 2867, 1466, 1362, 1179, 1123, 1050 cm^{-1}; HRMS calcd for $[C_{25}H_{40}OSiNa]^+$ 407.2741, found 407.2739. Data for the less polar diastereomer: R_f 0.8 (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65−5.54 (m, 2H), 5.51 (d, J = 3.3 Hz, 1H), 3.86 (s, 1H), 2.78−2.72 (m, 1H), 2.59 (t, J = 8.7 Hz, 1H), 1.91 (septet, J = 5.1 Hz, 1H), 1.76 (d, J = 12.9 Hz, 1H), 1.72−1.68 (m, 1H), 1.49 (dd, J = 13.5, 11.7 Hz, 2H), 1.46−1.42 (m, 1H), 1.24−1.18 (m, 1H), 1.12 (s, 3H), 1.08−1.05 (m, 21H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 129.6, 128.2, 125.5, 78.4, 64.8, 60.7, 49.6, 48.9, 45.7, 34.1, 29.1, 28.7, 26.6, 24.5, 22.9, 18.2, 18.1, 12.3; IR (neat) 3021, 2923, 2866, 1467, 1090, 1057, 1050 cm^{-1}. Anal. Calcd for $C_{25}H_{40}$: C 78.07, H 10.49. Found: C 78.04, H 10.45.

Alcohol 19. Cerium trichloride heptahydrate (15.4 g, 41.2 mmol) was added to a solution of enone **17** (7.1 g, 31.7 mmol) in methanol (200 mL) and stirred for 0.5 h. The reaction was cooled to −78 °C, sodium borohydride (1.52 g, 41.2 mmol) was added in five equal portions over 0.25 h and the suspension was stirred for an additional 2 h at −78 °C. A saturated solution of ammonium chloride (50 mL) was added and the reaction mixture slowly warmed to room temperature. Water (100 mL) was added and the mixture extracted with dichloromethane (3 × 100 mL). The combined organic extracts were concentrated under reduced pressure. Purification by flash chromatography (9:1 hexanes:ethyl acetate) yielded alcohol **19** as a white powder (6.2 g, 87%): R_f 0.3 (9:1 hexanes:ethyl acetate); mp 101−103 °C (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dd, J = 10.5, 6.5 Hz, 1H), 5.62 (dd, J = 11.0, 7.0 Hz, 1H), 5.56 (t, J = 2.5 Hz, 1H), 4.29 (br d, J = 4.5 Hz, 1H), 2.82 (td, J = 7.2, 3.2 Hz, 1H), 2.62 (t, J = 8.0 Hz, 1H), 1.92 (ddd, J = 12.8, 9.2, 5.2 Hz, 1H), 1.77 (ddd, J = 7.2, 5.6, 2.0 Hz, 1H), 1.64 (s, 2H), 1.51 (br d, J = 4.5 Hz, 1H), 1.49 (d, J = 13.0 Hz, 1H), 1.31−1.23 (m, 2H), 1.14 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 131.3, 125.2, 124.6, 79.5, 60.7, 60.5, 49.7, 48.8, 43.0, 33.2, 29.3, 28.7, 26.6, 22.7, 22.6; IR ($CHCl_3$) 3604, 3022, 2958, 2927, 2865, 1443, 1365, 1266, 1068 cm^{-1}; HRMS calcd for $[C_{16}H_{20}O]^+$ 228.1514, found 228.1514. The structure was further confirmed by X-ray analysis.

Dione 27. A solution of diol **24** (2.00 g, 4.8 mmol) in dichloromethane (10 mL) was added dropwise to a stirred solution of trifluoroacetic anhydride (2.8 mL, 19.7 mmol) and dimethyl sulfoxide (2.1 mL, 29.2 mmol) in 1:1 dichloromethane: THF (60 mL) at −78 °C. The reaction was stirred for 2 h at −78 °C and triethylamine (8.3 mL, 59 mmol) was added. The reaction was stirred for a further 1 h at −78 °C before being allowed to slowly warm to room temperature. The reaction mixture was quenched with water (100 mL) and diluted with dichloromethane (100 mL). The layers were separated and the organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (5:1 hexanes:ethyl ac-

(36) In the only available limited ^{1}H NMR data of 9-*epi*-pentalenic acid, the olefinic proton appeared at δ 6.87, see ref 7i.

(37) Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409−2410.

etate) yielded dione **27** as a yellow solid (1.85 g, 93%): R_f 0.55 (5:1 hexanes:ethyl acetate); mp 107−108 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (t, J = 2.4 Hz, 1H), 4.55 (d, J = 1.6 Hz, 1H), 3.66 (dd, J = 8.0, 3.2 Hz, 1H), 3.10 (t, J = 8.4 Hz, 1H), 2.34−2.27 (m, 2H), 2.05 (br d, J = 7.2 Hz, 2H), 1.97 (d, J = 14.8 Hz, 1H), 1.75 (d, J = 13.6 Hz, 1H), 1.70 (d, J = 14.4 Hz, 1H), 1.18 (s, 3H), 1.06−1.03 (m, 21H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 201.1, 164.6, 113.3, 79.9, 62.4, 60.1, 57.3, 49.3, 43.6, 42.0, 34.4, 34.2, 29.1, 28.4, 22.9, 18.5, 18.4, 13.0; IR ($CHCl_3$) 2946, 2868, 1716, 1680, 1182, 1123 cm^{-1}; HRMS calcd for $[C_{25}H_{38}O_3SiNa]^+$ 437.2482, found 437.2490. Anal. Calcd for $C_{25}H_{38}$: C 72.41, H 9.24. Found: C 72.15, H 9.15.

Carboxylic Acid 29. To a stirred solution of anhydride **28** (1.65 g, 3.86 mmol) in dichloromethane (80 mL) was added methanol (0.96 mL, 23.7 mmol) and triethylamine (1.35 mL, 9.70 mmol). The reaction was stirred at room temperature for 48 h and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, acidified with dilute HCl, washed with water and brine, and dried over anhydrous $MgSO_4$. Solvent evaporation followed by purification by flash chromatography (1:1 hexanes:ethyl acetate) yielded acid **29** as a white solid (1.58 g, 89%): R_f 0.5 (1:1 hexanes:ethyl acetate); mp 185−187 °C (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (dd, J = 2.5, 1.5 Hz, 1H), 4.50 (t, J = 2.0 Hz, 1H), 3.65 (s, 3H), 3.62 (t, J = 2.5 Hz, 1H), 3.29 (dt, J = 11.2, 6.4 Hz, 1H), 2.44 (ddd, J = 15.0, 6.5, 1.5 Hz, 1H), 2.20 (ddd, J = 12.0, 10.0, 7.2 Hz, 1H), 2.01 (dd, J = 13.2, 7.6 Hz, 1H), 1.83 (d, J = 13.0 Hz, 1H), 1.69 (dd, J = 9.0, 7.0 Hz, 1H), 1.63 (dd, J = 9.0, 7.5 Hz, 1H), 1.40 (d, J = 12.5 Hz, 1H), 1.22 (s, 3H), 1.12−1.06 (m, 21H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 173.4, 151.8, 118.3, 78.8, 61.9, 55.4, 54.7, 54.1, 51.5, 42.4, 36.6, 30.3, 30.1, 27.3, 26.4, 25.8, 18.5, 12.8; IR ($CHCl_3$) 2947, 1728, 1707, 1463, 1220, 1132 cm^{-1}; HRMS calcd for $[C_{26}H_{42}O_5SiNa]^+$ 485.2694, found 485.2686. Anal. Calcd for $C_{26}H_{42}$: C 67.49, H 9.15. Found: C 67.56, H 8.99.

Lactones 30 and 31. Method I: To a stirred solution of acid **29** (2 g, 4.3 mmol) in dichloromethane (300 mL) was added a solution of 57% hydriodic acid in water (1.8 mL, 4.4 mmol) and the resultant solution was stirred for 2 h at room temperature. A saturated solution of sodium sulfite (100 mL) was added, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (hexanes:ethyl acetate 3:1 to 1:1) yielded lactone **30** as a white powder (1.64 g, 82%): R_f 0.3 (2:1 hexanes: ethyl acetate); mp 170−171 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (s, 1H), 3.65 (s, 3H), 3.17 (td, J = 9.6, 7.2 Hz, 1H), 3.03 (dt, J = 11.6, 7.6 Hz, 1H), 2.62 (dd, J = 16.4, 10.8 Hz, 1H), 2.58 (dd, J = 16.4, 10.8 Hz, 1H), 2.12 (ddd, J = 14.8, 9.6, 6.4 Hz, 1H), 2.03−1.94 (m, 1H), 1.95 (d, J = 8.4 Hz, 1H), 1.91 (d, J = 5.6 Hz, 1H), 1.86 (d, J = 8.6 Hz, 1H), 1.69 (d, J = 13.6 Hz, 1H), 1.31 (ddd, J = 14.4, 10.4, 1.6 Hz, 1H), 1.21 (s, 3H), 1.20−1.08 (m, 21H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 169.4, 103.4, 87.5, 62.1, 52.7, 52.1, 47.4, 41.7, 39.5, 37.0, 32.2, 31.2, 29.7, 27.9, 26.3, 23.7, 18.6, 18.5, 13.0; IR (neat) 2947, 2862, 1728, 1707, 1246, 1132 cm^{-1}; HRMS calcd for $[C_{26}H_{42}O_5SiNa]^+$ 485.2694, found 485.2686. Iodide **31** (0.3 g, 15%): R_f 0.7 (2:1 hexanes:ethyl acetate); mp 156−158 °C (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (dd, J = 11.5, 6.0 Hz, 1H), 3.95 (s, 1H), 3.68 (s, 3H), 3.34 (ddd, J = 18.0, 9.0, 1.5 Hz, 1H), 3.01 (dd, J = 15.0, 7.0 Hz, 1H), 2.83 (dd, J = 14.5, 8.5 Hz, 1H), 2.56 (dd, J = 16.0, 5.5 Hz, 1H), 2.50 (dd, J = 12.0, 5.5 Hz, 1H), 2.40 (dd, J = 16.0, 5.0 Hz, 1H), 2.26−2.19 (m, 2H), 2.12 (d, J = 14.0 Hz, 1H), 2.09−2.02 (m, 1H), 1.87 (d, J = 14.0 Hz, 1H), 1.16−1.10 (m, 3H), 1.07 (s, 3H), 1.06 (s, 15H), 1.05 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 168.9, 102.9, 89.4, 57.1, 56.9, 55.3, 52.2, 52.1, 44.4, 42.0, 40.5, 37.4, 31.2, 30.2, 26.6, 22.5, 18.5, 13.1; IR (neat) 2945, 1738, 1463, 1258, 1120, 883 cm^{-1}; HRMS calcd for $[C_{26}H_{43}IO_5SiNa]^+$ 613.1817, found 613.1825. The structure was further confirmed by X-ray analysis.

Method II: To a stirred solution of acid **29** (19 mg, 43.0 μmol) in dichloromethane (3 mL) was added a solution of 57% hydriodic in water (55.0 μL, 0.13 mmol) and the mixture was stirred for 24 h at room temperature. A saturated solution of sodium sulfite was added and the product was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. Solvent evaporation followed by purification by flash chromatography (hexanes: ethyl acetate 3:1 to 1:1) afforded lactone **30** (3.7 mg, 19%) and iodide **31** (10.2 mg, 40%).

1,7,7-Trimethyl-6-oxo-decahydrocyclopenta[*c*]pentalene-4-carboxylic Acid Methyl Ester (40). Tributyltin hydride (0.46 mL, 1.68 mmol) and AIBN (22.8 mg, 0.14 mmol) were added to a solution of ketone **38** (0.26 g, 0.85 mmol) in toluene (55 mL). A vigorous stream of argon was bubbled through the solution for 0.5 h and the solution was purged and back-filled two times. The solution was refluxed for 2 h and allowed to cool to room temperature. Concentration under reduced pressure yielded crude acid **39**, which was used directly for the next step without further purification.

2,2′ Dithiopyridine-1,1-dioxide[34] (0.25 g, 1.0 mmol) and triphenylphosphine (0.27 g, 1.03 mmol) were added to a solution of crude acid **39** [assumed quantitative yield from previous step] in dichloromethane (81 mL) and the solution was stirred for 0.5 h at room temperature in the dark. *tert*-Butyl thiol (0.28 mL, 2.56 mmol) was added, and the solution was irradiated for 15 min with a 150 W tungsten lamp and concentrated under reduced pressure. Purification by thick layer chromatography (1:1 hexanes:CH_2Cl_2 to CH_2Cl_2) furnished keto-ester **40** (0.19 g, 86% over two steps) as a colorless oil: R_f 0.3 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 2.67−2.63 (m, 2H), 2.53−2.48 (m, 1H), 2.32−2.26 (m, 1H), 2.14 (d, J = 14.4 Hz, 1H), 2.16−2.09 (m, 1H), 1.88−1.74 (m, 3H), 1.85 (d, J = 13.6 Hz, 1H), 1.52−1.47 (m, 1H), 1.24−1.18 (m, 1H), 1.15 (s, 3H), 1.07 (s, 3H), 0.97 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 224.6, 175.6, 59.0, 58.1, 54.1, 52.8, 52.2, 51.6, 46.4, 45.8, 35.0, 34.9, 32.0, 27.7, 27.0, 15.8; IR ($CHCl_3$) 2928, 2852, 1729, 1198, 1170, 1075 cm^{-1}; HRMS calcd for $[C_{16}H_{24}O_3Na]^+$ 287.1618, found 287.1614.

6-Hydroxy-1,7,7-trimethyldecahydrocyclopenta[*c*]pentalene-4-carboxylic acId Methyl Ester (47). To a solution of **46** (40 mg, 0.16 mmol) in THF (5 mL) was added NaH (11.5 mg, 0.48 mmol) at 0 °C and the solution was stirred for 30 min. After the mixture was cooled to −78 °C, anhydrous liquid ammonia (40 mL), anhydrous methanol (2 mL), and lithium foil (34 mg, 4.9 mmol) were added and the reaction was stirred at the same temperature for 0.5 h. A saturated solution of ammonium chloride (10 mL) was added, and ammonia was allowed to evaporate. The residue was carefully acidified with 1 M hydrochloric acid at 0 °C and the product was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure.

The crude residue was dissolved in methanol (5.0 mL) and stirred with $TMSCHN_2$ (0.16 mL of 2 M solution in hexane, 0.32 mmol) for 0.5 h. Acetic acid (0.2 mL) was added and the solution concentrated under reduced pressure. Purification by thick layer chromatography (2:1 cyclohexane:ethyl acetate) yielded ester **47** (32 mg, 75%) as a white solid: R_f 0.65 (1:1 cyclohexane:ethyl acetate); mp (hexane) 107−109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.26 (d, J = 9.5 Hz, 1H), 3.02−2.96 (m, 1H), 2.27 (dd, J = 16.5, 8.0 Hz, 1H), 2.15 (t, J = 6.5 Hz, 1H), 1.93−1.85 (m, 3H), 1.71 (d, J = 13.5 Hz, 1H), 1.69−1.63 (m, 1H), 1.56 (d, J = 13.5 Hz, 1H), 1.53−1.48 (m, 1H), 1.46 (br s, 1H), 1.30−1.19 (m, 2H), 0.98 (s, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 85.5, 58.7, 58.1, 55.1, 51.7, 50.4, 45.9, 45.7, 41.8, 35.9, 31.8, 27.6, 27.0, 20.7, 17.0; IR (neat) 3443, 2950, 1736, 1595, 1460, 1172 cm^{-1}; HRMS calcd for $[C_{16}H_{26}O_3Na]^+$ 289.1774,

found 289.1770. The assigned structure was further confirmed by X-ray analysis.

Methyl-9-*epi*-pentalenate (49). To a solution of ester **48** (28 mg, 0.07 mmol) in dry THF (3 mL) was added LDA [prepared from diisopropylamine (52 μL, 0.37 mmol) and 1.6 M BuLi (0.22 mL, 0.37 mmol) in THF (2 mL)] at −78 °C and the mixture was stirred for 30 min at the same temperature and at 0 °C for 15 min. After the mixture was cooled to −78 °C, a solution of PhSeCl (70 mg, 0.37 mmol in 1 mL of THF) was added and the reaction mixture was stirred for another 3 h at −78 °C. The reaction was quenched with water and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with 10% HCl, water, and brine and dried over anhydrous $MgSO_4$. Solvent evaporation followed by purification by thick layer chromatography (20:1 cyclohexane: ethyl acetate) furnished the crude seleno-ester, which was used directly for the next step.

To this crude seleno-ester in THF (3 mL) at 0 °C were added glacial acetic acid (44 μL, 0.73 mmol) and 30% H_2O_2 (83 μL, 0.73 mmol) and the resulting solution was stirred at the same temperature for 1 h. The product was extracted with ethyl acetate and the organic layer was washed with saturated $NaHCO_3$ solution, water, and brine and dried over anhydrous $MgSO_4$. Solvent evaporation furnished the crude product, which was directly used for the desilylation reaction.

To a solution of this crude ester in dry THF (2 mL) was added a 1 M solution of TBAF in THF (0.21 mL, 0.21 mmol) and the mixture was stirred for 24 h. THF was evaporated and the residue was dissolved in ethyl acetate, washed with water and brine, and dried over anhydrous $MgSO_4$. Solvent evaporation followed by purification by thick layer chromatography (2:1 hexanes:ethyl acetate) furnished ester **49** (10.2 mg, 53%) as a colorless oil: R_f 0.3 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (t, J = 2.0 Hz, 1H), 3.72 (s, 3H), 3.54 (d, J = 2.0 Hz, 1H), 3.13 (dd, J = 7.5, 1.5 Hz, 1H), 3.0 (dd, J = 5.5, 2.5 Hz, 1H), 1.86 (d, J = 13.0 Hz, 1H), 1.83−1.71 (m, 2H), 1.61 (d, J = 13.5 Hz, 1H), 1.67−1.57 (m, 2H), 1.51 (br s, 1H, OH), 1.10−0.91 (m, 1H), 0.99 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 146.1, 138.7, 84.5, 61.9, 60.4, 59.4, 52.1, 51.6, 44.9, 43.8, 33.1, 30.4, 27.1, 23.9, 14.8; IR (neat) 3436, 2952, 1717, 1629, 1238 cm^{-1}; HRMS cacld for $[C_{16}H_{24}O_3Na]^+$ 287.1618, found 287.1619.

9-*epi*-Pentalenic Acid. To a solution of ester **49** (8 mg, 30 μmol) in MeOH (3 mL) was added 10% aq KOH (0.5 mL) and the resulting solution was heated at 55 °C for 3 h. MeOH was evaporated and the residue acidified with 10% HCl at 0 °C. The product was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. Solvent evaporation followed by purification by thick layer chromatography (ethyl acetate) furnished acid **2** (7.2 mg, 95%) as a colorless oil: R_f 0.4 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, J = 2.0 Hz, 1H), 3.57 (d, J = 2.0 Hz, 1H), 3.13 (d, J = 8.5 Hz, 1H), 3.03 (d, J = 2.5 Hz, 1H), 1.87 (d, J = 13.5 Hz, 1H), 1.83−1.67 (m, 3H), 1.63 (d, J = 13.0 Hz, 1H), 1.64−1.58 (m, 1H), 1.04−0.97 (m, 1H), 1.0 (s, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 148.9, 138.2, 84.4, 62.0, 60.5, 59.1, 52.1, 44.9, 43.9, 33.1, 30.3, 27.0, 23.8, 14.8; IR (neat) 3379, 2926, 1687, 1630, 1461 cm^{-1}; HRMS calcd for $[C_{15}H_{22}O_3Na]^+$ 273.1461, found 273.1458.

Acknowledgment. The authors wish to thank National Institute of Health for their generous support of this research through grant GM-30771.

Supporting Information Available: Experimental details and characterization data for all relevant compounds, ^{1}H spectra for compounds **2**, **17**−**20**, **24**, **27**−**32**, **34**−**38**, **40**, and **43**−**49** and ^{13}C NMR spectra for compounds **2**, **17**−**19**, **24**, **28**−**32**, **34**, **36**, **44**, **45**, **47**−**49**, as well as a CIF file containing X-ray crystallographic data for compounds **19**, **31**, deprotected **33**, and **47**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO040204O