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Stereoselective Synthesis of (−)-Acanthoic Acid

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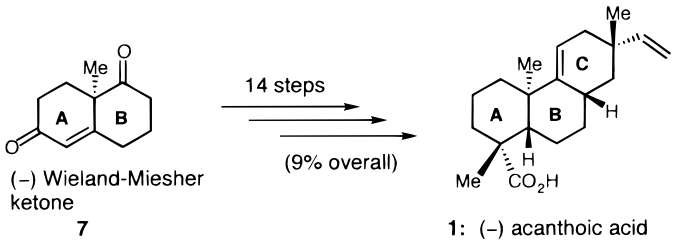
ABSTRACT

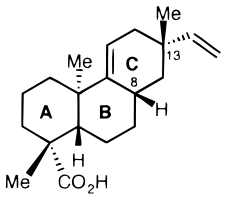


(−) Wieland-Miesher ketone
7

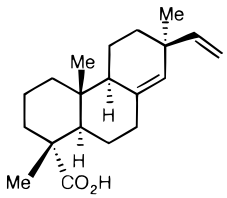
1: (−) acanthoic acid

The first stereoselective synthesis of (−)-acanthoic acid (1) has been designed and accomplished. Our synthetic plan departs from (−) Wieland−Miesher ketone (7) and calls upon a Diels−Alder cycloaddition reaction for the construction of the C ring of 1. The described synthesis confirms the proposed stereochemistry of 1 and represents an efficient entry into an unexplored class of biologically active diterpenes.

The root bark of *Acanthopanax koreanum* Nakai (Araliaceae), a deciduous shrub that grows in the Republic of Korea, has been used traditionally as a tonic, a sedative, and a remedy for rheumatism and diabetes.[1] In their study of the pharmacologically active extracts of this folk medicine, Chung and co-workers have isolated and structurally characterized a novel diterpene, (−)-pimara-9(11),15-dien-19-oic acid, which was subsequently named acanthoic acid (**1**).[2]



1: (−) acanthoic acid



2: (+) pimaric acid

From the biosynthesis standpoint, **1** belongs to a rather large family of pimaradiene diterpenes, which may be best represented by pimaric acid (**2**).[3] Interestingly, however, the structure of acanthoic acid is distinguished by an uncommon connectivity across the rigid tricyclic core, which may be held accountable for its pharmacological profile. Indeed, the recent isolation of this compound has allowed studies into its biological activity and verified its medicinal potential.[2b,c] More specifically, acanthoic acid was found to exhibit promising antiinflammatory and antifibrotic activities that presumably arise by inhibiting the production of the pro-inflammatory cytokines: tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1).[4] This inhibition was concentration dependent and cytokine-specific since under the same conditions the production of IL-6 or IFN-γ (interferon-gamma) were not affected. In addition, acanthoic acid was found to be active upon oral administration in animal models and showed minimal toxicity in experiments performed in mice.

(1) *Medicinal Plants of East and Southeast Asia*; Perry, L. M., Metzger, J., Eds.; MIT Press: Cambridge, MA and London, 1980.

(2) (a) Kim, Y.-H.; Chung, B. S.; Sankawa, U. *J. Nat. Prod.* **1988**, *51*, 1080−1083. (b) Kang, H.-S.; Kim, Y.-H.; Lee, C.-S.; Lee, J.-J.; Choi, I.; Pyun, K.-H. *Cellular Immunol.* **1996**, *170*, 212−221. (c) Kang, H.-S.; Song, H. K.; Lee, J.-J.; Pyun, K.-H.; Choi, I. *Mediators Inflammation* **1998**, *7*, 257−259.

(3) Ruzicka, L.; Sternbach, L. *J. Am. Chem. Soc.* **1948**, *70*, 2081−2085. Ireland, R. E.; Schiess, P. W. *Tetrahedron Lett.* **1960**, *25*, 37−43. Wenkert, E.; Buckwalter, B. L. *J. Am. Chem. Soc.* **1972**, *94*, 4367−4372. Wenkert, E.; Chamberlin, J. W. *J. Am. Chem. Soc.* **1959**, *81*, 688−693.

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The combination of uncommon structure and promising pharmacological activity displayed by **1** prompted us to extend our synthetic studies[5] to this family of biologically important metabolites. In this paper we report a stereoselective total synthesis of (−)-acanthoic acid. In addition to constituting the inaugural synthetic entry into this class of bioactive diterpenes,[6] our studies confirm the structure and absolute stereochemistry of **1**.

The retrosynthetic strategy toward acanthoic acid is illustrated in Figure 1. The C ring of **1** was envisioned to be

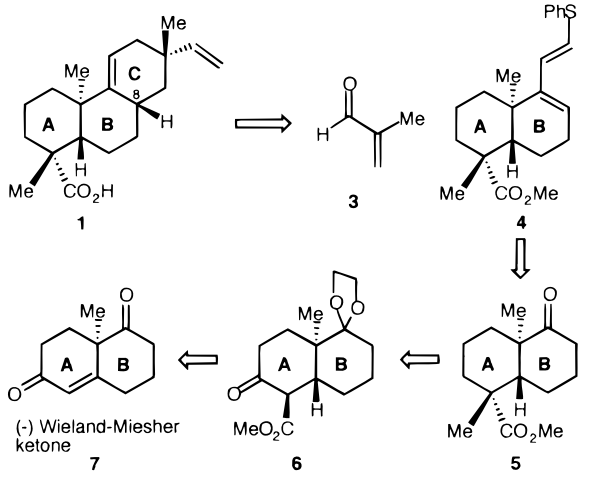
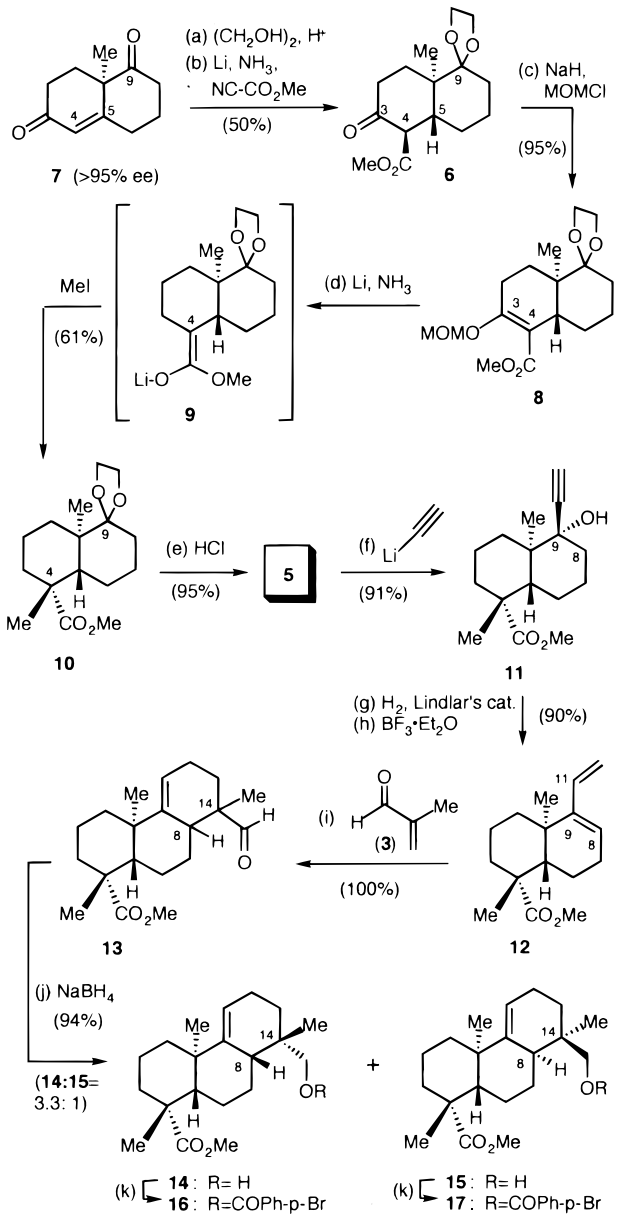


Figure 1. Retrosynthetic analysis of (−)-acanthoic acid (**1**).

constructed by a Diels−Alder cycloaddition reaction, thereby revealing dienophile **3** and an appropriately substituted diene, such as **4**, as ideal coupling partners.[7] If successful, this reaction could introduce both the unsaturation at the C9−C11 bond and the desired stereochemistry at the C8 and C13 carbons. Diene **4** could be produced by functionalization of ketone **5**, whose C4 quaternary center was projected to be formed by a stereocontrolled alkylation of β-ketoester **7**. This analysis suggested the use of (−) Wieland−Miesher ketone **7** as a putative starting material. Application of such a plan to the synthesis of acanthoic acid is shown in the Scheme 1.[8]

Scheme 1. Studies toward the Tricyclic Core of **1**[a]



[a] Reagents and conditions: (a) 0.1 equiv of PTSA, 1.05 equiv of $(CH_2OH)_2$, benzene, 80 °C, 4 h, 90%; (b) 2.2 equiv of Li, liquid NH_3, 1.0 equiv of *t*-BuOH, −78 to −30 °C, 30 min then isoprene (excess), −78 to 50 °C; 1.1 equiv of NC−CO_2Me, Et_2O, −78 to 0 °C, 2 h, 55%; (c) 1.1 equiv of NaH, HMPA, 25 °C, 3 h; 1.1 equiv of MOMCl, 25 °C, 2 h, 95%; (d) 7.0 equiv of Li, liquid NH_3, −78 to −30 °C, 20 min; CH_3I (excess), −78 to −30 °C, 1 h, 61%; (e) 1 N HCl, THF, 25 °C, 15 min, 95%; (f) 1.6 equiv of Li acetylide, Et_2O, 25 °C, 1 h, 91%; (g) Lindlar's catalyst (20% per weight), H_2, dioxane/pyridine, 10/1 25 °C, 10 min, 95%; (h) 4.4 equiv of BF_3•Et_2O, benzene/THF: 4/1, 80 °C, 5 h, 95%; (i) 13 equiv of **3**, neat, 8 h, 25 °C, 100%; (j) 1.4 equiv of $NaBH_4$, THF/MeOH:10/1, 30 min, 25 °C, 94% (**14**:**15** = 3.3:1); (k) 1.1 equiv of *p*-Br-C_6H_4COCl, 1.5 equiv of pyridine, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C, 2 h, 95% for **16**, 97% for **17**.

Our synthetic venture departed with optically pure enone **7**, which was readily available through a D-proline-mediated asymmetric Robinson annulation (75−80% yield, >95% ee).[9]

(4) For recent reviews on TNF-α and IL-1, see: *Tumor Necrosis Factors. The Molecules and their Emerging Role in Medicine*; Beutler, B., Ed.; Raven Press: New York, 1992. Aggarwal, B.; Puri, R. *Human Cytokines: Their Role in Disease and Therapy*; Blackwell Science, Inc.: Cambridge, MA, 1995. Thorpe, R.; Mire-Sluis, A. *Cytokines*; Academic Press: San Diego, 1998. Kurzrock, R.; Talpaz, M. *Cytokines: Interleukins and Their Receptors*; Kluwer Academic Publishers: Boston, 1995. Szekanecz, Z.; Kosh, A. E.; Kunkel, S. L.; Strieter, R. M. *Clin. Pharmacol.* **1998**, *12*, 377−390. Camussi, G.; Lupin, E. *Drugs* **1998**, *55*, 613−620. Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **1999**, *42*, 2295−2314.

(5) For related recent syntheses from our laboratories, see: Xiang, A. X.; Watson, D. A.; Ling. T.; Theodorakis, E. A. *J. Org. Chem.* **1998**, *63*, 6774−6775. Ling, T.; Xiang, A. X.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3089−3091.

(6) For synthetic studies toward **1**, see: Suh, Y.-G.; Park, H.-J.; Jun, R.-O. *Arch. Pharm. Res.* **1995**, *18*, 217−218. Suh, Y.-G.; Jun, R.-O.; Jung, J.-K.; Ryu, J.-S. *Synth. Commun.* **1997**, *27*, 587−593.

(7) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Oxford, NY; Pergamon Press: 1991; pp 315−399.

Selective ketalization of the C9 ketone group of **7**, followed by reductive alkylation across the enone functionality with methyl cyanoformate, afforded ketoester **6** in 50% overall yield.[10] To introduce the desired functionalization at the C4 position we sought to implement a second reductive alkylation procedure, originally reported by Coates and Shaw.[11] With this in mind, compound **6** was first transformed to the corresponding methoxymethyl ether **8**, which upon treatment with lithium in liquid ammonia and iodomethane gave rise to ester **10** in 58% overall yield and as a single diastereomer.[12] It was expected that the stereoselectivity of this addition would arise from the strong preference of the presumed intermediate enolate **9** to undergo alkylation at the less hindered equatorial side. Nonetheless, unambiguous confirmation of this structure was deferred until assembly of the entire backbone of acanthoic acid.

With the bicyclic core in hand, our attention shifted toward construction of the C ring, which was projected to be formed via a Diels−Alder reaction between methacrolein (**3**) and the sulfur-containing diene **4**. The synthesis of **4** was initiated with an acid-catalyzed deprotection of the C9 ketal of **10**, followed by alkylation of the resulting ketone **5** with lithium acetylide·ethylenediamine complex.[13] This sequence afforded alkyne **11** as an 8:1 diasteromeric mixture at C9 (in favor of the isomer shown) and in 86% overall yield. At this point, it was deemed important to examine the diastereofacial selectivity of the Diels−Alder reaction and evaluate the overall feasibility of our plan using a nonfunctionalized diene, such as **12**. To this end, the diastereomeric mixture of propargyl alcohols **11** was partially reduced (H_2, Lindlar's catalyst) and dehydrated (BF_3·Et_2O) to produce diene **12** in 90% yield.[14] The Diels−Alder cycloaddition between **12** and methacrolein (**3**) proceeded smoothly under neat conditions at 25 °C and afforded in quantitative yield a mixture of two diastereomeric aldehydes that could be separated only after reduction with sodium borohydride. The resulting alcohols **14** and **15** (3.3:1 in favor of **14**) were transformed to the corresponding *p*-bromobenzoate esters (**16** and **17**, respectively), which upon recrystallization with dichloromethane/ethanol yielded crystals suitable for X-ray analysis (Figure 2).

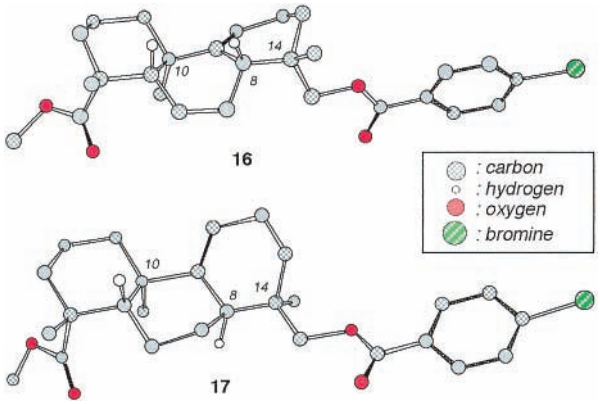


Figure 2. Chem3D representation of ORTEP drawings of **16** and **17**. (For clarity only selected hydrogens are shown.)

The results of the X-ray studies were instrumental in several ways. First, they established that the tricyclic system had the expected stereochemistry at the C4 position and confirmed that the Diels−Alder reaction proceeded with exclusive *endo* orientation.[15] Second, after reduction, the major product of the cycloaddition was shown to be alcohol **14**, which had the desired stereochemistry at the C8 center, thereby demonstrating a strong preference for diene **12** to undergo reaction with **3** from the α-face (bottom side attack). Moreover, these data indicated that synthesis of acanthoic acid would require an inversion in the orientation of the incoming dienophile. In principle, this could be accomplished by altering the atomic orbital coefficients at the termini of the diene, supporting the use of a heteroatom-containing diene, such as **4**, during the cycloaddition.[16] The construction of diene **4** and its utilization for the synthesis of **1** is shown in Scheme 2.

Compound **4** was produced by a radical addition of thiophenol onto alkyne **11**,[17] followed by $POCl_3$-mediated dehydration of the resulting allylic alcohol[18] (two steps, 70% yield). Interestingly, this dehydration was also attempted with BF_3·Et_2O but proved ineffective in this case. With a substantial amount of **4** in hand, we investigated the Diels−Alder reaction, using **3** as the dienophile. Several thermal (−78 to 80 °C) and Lewis acid (BF_3·Et_2O, $TiCl_4$, $AlCl_3$, and $SnCl_4$) catalyzed Diels−Alder conditions were tested. Best results were obtained with $SnCl_4$ in methylene chloride at −20 °C and afforded aldehyde **18** in 84% yield as a 4.2:1 mixture of diastereomers. To simplify the product characterization and allow adequate separation, this mixture was reduced with $NaBH_4$ and reductively desulfurized using

(8) All new compounds exhibited satisfactory spectral and analytical data (see Supporting Information).

(9) Buchschacher, P.; Fuerst, A.; Gutzwiller, J. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. 7, pp 368−3372.

(10) Crabtree, S. R.; Mander, L. N.; Sethi, P. S. *Org. Synth.* **1992**, 70, 256−263.

(11) Coates, R. M.; Shaw, J. E. *J. Org. Chem.* **1970**, *35*, 2597−2601. Coates, R. M.; Shaw, J. E. *J. Org. Chem.* **1970**, *35*, 2601−2605.

(12) For selected applications of this method to the synthesis of other diterpenes, see: Welch, S. C.; Hagan, C. P. *Synth. Commun.* **1973**, *3*, 29−32. Welch, S. C.; Hagan, C. P.; Kim, J. H.; Chu, P. S. *J. Org. Chem.* **1977**, *42*, 2879−2887. Welch, S. C.; Hagan, C. P.; White, D. H.; Fleming, W. P.; Trotter, J. W. *J. Am. Chem. Soc.* **1977**, *99*, 549−556.

(13) Das, J.; Dickinson, R. A.; Kakushima, M.; Kingston, G. M.; Reid, G. R.; Sato, Y.; Valenta, Z. *Can. J. Chem.* **1984**, *62*, 1103−1111.

(14) Coisne, J.-M.; Pecher, J.; Declercq, J.-P.; Germain, G.; van Meerssche, M. *Bull. Soc. Chim. Belg.* **1980**, *89*, 551−557.

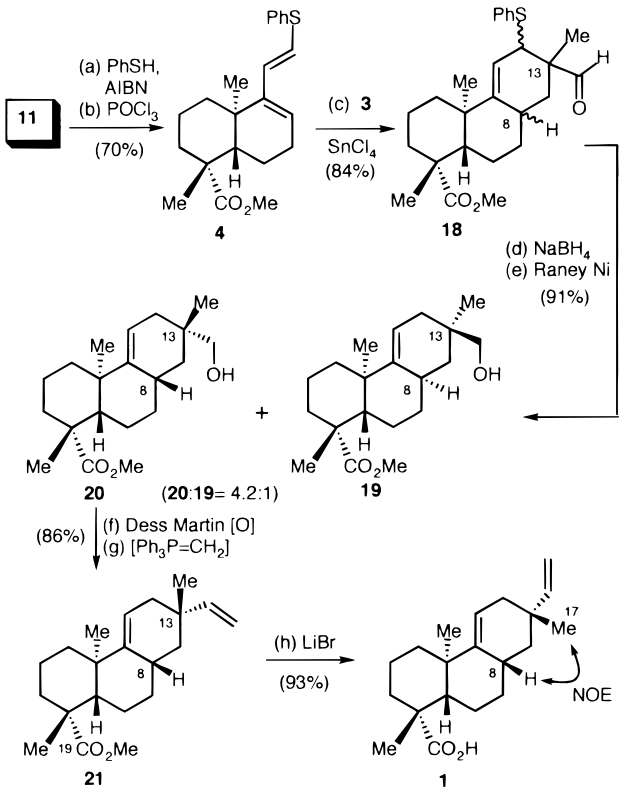
(15) Interestingly, methacrolein was shown to produce *exo* Diels−Alder products when reacting with cyclopentadiene: Kobuke, Y.; Fueno, T.; Furukawa, J. *J. Am. Chem. Soc.* **1970**, *92*, 6548−6553. This unusual observation was rationalized on the basis of the steric repulsion exhibited by the methyl group: Yoon, T.; Danishefsky, S. J.; de Gala, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 853−855.

(16) For use of sulfur-containing dienes in Diels−Alder reactions, see: Overman, L. E.; Petty, C. B.; Ban, T.; Huang, G. T. *J. Am. Chem. Soc.* **1983**, *105*, 6335−6338. Trost, B. M.; Ippen, J.; Vladuchick, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 8116−8118. Cohen, T.; Kozarych, Z. *J. Org. Chem.* **1982**, *47*, 4008−4010. Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208−1217. Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753−786.

(17) Greengrass, C. W.; Hughman, J. A.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1985**, 889−890.

(18) Trost, B. M.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 7910−7925. Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443−3452.

Scheme 2. Synthesis of Acanthoic Acid (**1**)[a]



[a] Reagents and conditions: (a) 3.0 equiv of PhSH, 0.05 equiv of AIBN, xylenes, 120 °C, 18 h, 86%; (b) 1.1 equiv of $POCl_3$, HMPA, 25 °C, 1 h; 1.1 equiv of pyridine, 150 °C, 18 h, 81%; (c) 3.0 equiv of **3**, 0.2 equiv of $SnCl_4$ (1 M in CH_2Cl_2), CH_2Cl_2, −20 to 0 °C, 20 h, 84%; (d) 1.4 equiv of $NaBH_4$, EtOH, 25 °C, 30 min; (e) Raney Ni (excess), THF, 65 °C, 10 min, 91% (over two steps); (f) 1.3 equiv of Dess−Martin periodinane, CH_2Cl_2, 25 °C, 30 min; (g) 2.7 equiv of Ph_3PCH_3Br, 2.2 equiv of NaHMDS (1.0 M in THF), THF, 25 °C, 18 h, 86% (over two setps); (h) 3.0 equiv of LiBr, DMF, 160 °C, 3 h, 93%.

Raney Ni. Alcohols **19** and **20** (**19**:**20** = 1:4.2) were thus obtained in 91% overall yield. The structure of these compounds was assigned by comparison to the structures of the products isolated from the reaction of **3** and **12**. Treatment of major diastereomer **20** with Dess−Martin periodinane, followed by Wittig methylenation, installed the alkene functionality at the C13 center and produced **21** in 86% overall yield. The final step of our synthesis was deprotection of the C-19 carboxylic acid. The initially examined saponification methods failed, presumably due to steric hindrance created by the nearby methyl group and the axial orientation of the acid function. Gratifyingly, exposure of **21** to LiBr in refluxing DMF gave rise to acanthoic acid **1** in 93% yield, presumably via an S_N2-type displacement of the acyloxyl functionality.[19] Synthetic **1** had spectroscopic and analytical data identical to those reported for the natural product.[20] In addition, synthetic acanthoic acid (**1**) was found to inhibit TNF-α and IL-1β synthesis, similar to the inhibition reported for the natural product.[2b,c]

In conclusion, we present herein a concise, stereoselective synthesis of acanthoic acid (**1**). The synthetic strategy is highlighted by the implementation of a Diels−Alder reaction between diene **4** and methacrolein (**3**), which set the stereochemistry at the C13 and C8 carbon centers. The described synthesis of **1** requires 14 steps (starting with enone **7**) and proceeds in 9% overall yield. Moreover, the overall efficiency and versatility of our strategy sets the foundation for the preparation of designed analogues with improved pharmacological profiles.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **1**, **4**−**6**, **8**, **10**−**11**, **14**−**17**, and **20**−**21** and X-ray data for compounds **16**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Bennet, C. R.; Cambie, R. C. *Tetrahedron* **1967**, *23*, 927−941.

(20) Additional evidence for the desired relative stereochemistry of the C ring of **1** was obtained by NOE difference experiments, which showed that H17 and H8 are located at the same face of the tricyclic scaffold.