A Convergent Total Synthesis of the Michellamines[||]

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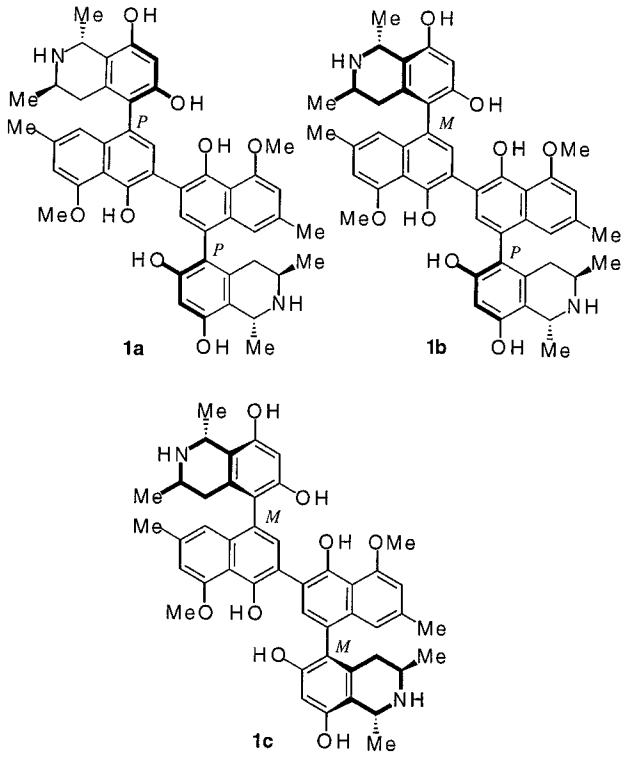
A convergent total synthesis of the anti-HIV michellamines (**1**) is described. The tetraaryl skeleton of the michellamines was constructed by formation first of the inner (nonstereogenic) biaryl axis and subsequently of the two other (stereogenic) axes in a highly convergent manner. The key transformation features a double Suzuki-type cross-coupling reaction between binaphthalene ditriflate **26** and isoquinolineboronic acid **35**. Ditriflate **26** is synthesized in six steps starting from diene **6** and 2,6-dibromobenzoquinone (**9**) in 21% overall yield. For large scale production of **26**, a substantially shortened version of an existing procedure for the preparation of bisnaphthoquinone **13** was also developed, which allows for the preparation of **13** from benzoquinone and diene **6** in five steps and 67% overall yield. Binaphthoquinone **13** was subsequently converted into ditriflate **26** in three steps and 67% overall yield. By the described synthetic strategy, michellamines A (**1a**) and B (**1b**) are produced (**1a**:**1b** = 1:2.5) in 24.6% overall yield from diene **6**. Curiously, none of the nonnaturally occurring atropoisomer **1c** is formed.

Introduction

The lack of effective drugs for the treatment of AIDS led the United States National Cancer Institute to initiate in the late 1980s a major effort to discover novel HIV (human immunodeficiency virus) inhibitory agents from natural sources.[1] In 1991, Boyd et al.[2,3] reported the isolation of two anti-HIV alkaloids, michellamines A and B, from the tropical plant *Ancistrocladus korupensis* native to Cameroon. Michellamine B, the more potent and abundant of the naturally occurring michellamines, aborted viral replication and virus-induced cell killing across an unusually broad range of HIV strains and isolates in diverse human host-cell types.[3]

By a combination of spectroscopic and degradative studies[2−6] michellamines A and B were assigned structures **1a** and **1b**, respectively, with the relative and absolute configurations shown. Initially, the third possible atropisomer named michellamine C (**1c**) was also isolated, but was later found to be an artifact formed under too harsh isolation conditions.[3,7]



The isolation of michellamine C (**1c**) apparently results from the fact that the michellamines can be interconverted by epimerization under basic conditions.[3] At equilibrium the ratio of michellamines A, B, and C is ~3:3:1. Although michellamine C (**1c**) is thermodynamically

[||] Part 102 in the series Acetogenic Naphthylisoquinoline Alkaloids (from the University of Würzburg). For part 101, see: Bringmann, G.; Saeb, W.; Wenzel, M.; François, G.; Schlauer, J. *Pharm. Pharmacol. Lett.*, submitted. Part 47 in the series: HIV-Inhibitory Natural Products (from the National Cancer Institute). For part 46, see: Hallock, Y. F.; Cardellina, J. H., II; Schäffer, M.; Bringmann, G.; Boyd, M. R. *BioMed. Chem. Lett.*, submitted.

[†] Institute für Organische Chemie.

[‡] National Cancer Institute.

[§] Boston College.

(1) Boyd, M. R. In *AIDS Etiology, Diagnosis, Treatment and Prevention*; De Vita, V. T., Jr., Hellman, S., Rosenberg, S. A., Eds.; Lippincott: Philadelphia, 1988, p 305.

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(6) Bringmann, G.; Gulden, K.-P.; Hallock, Y. F.; Manfredi, K. P.; Cardellina, J. H., II; Boyd, M. R.; Kramer, B.; Fleischhauer, J. *Tetrahedron* **1994**, *50*, 7807.

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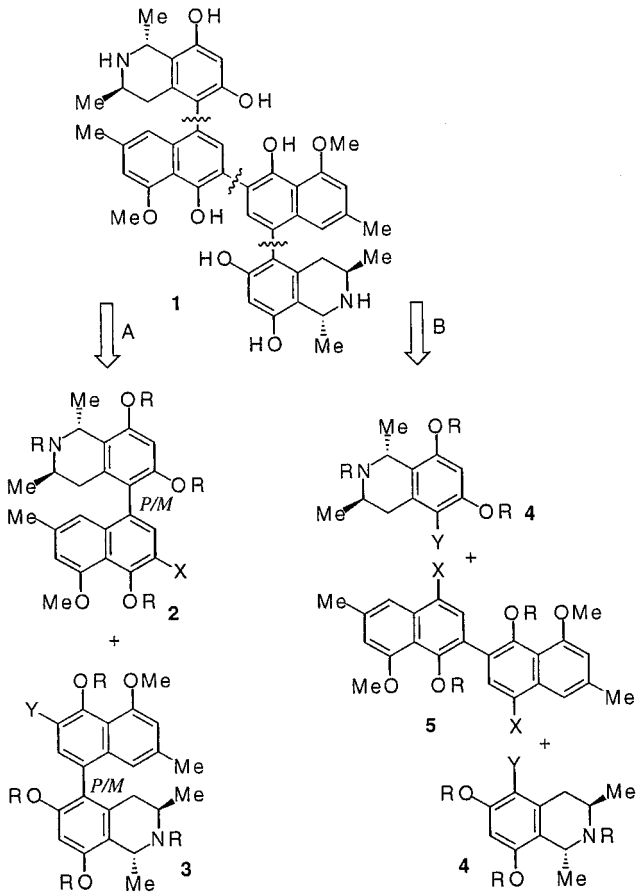
Scheme 1

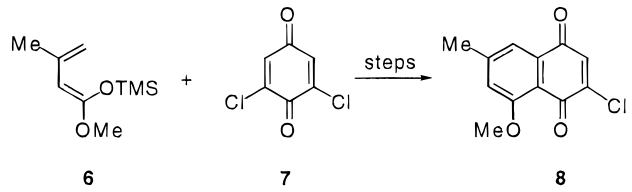


less stable than the other two atropisomers, the reason for the apparent total absence of **1c** in nature is unknown.

The pronounced biological activity as well as the structural novelty of the michellamines has attracted much interest from synthetic chemists, especially after the U.S. National Cancer Institute published[8] an announcement encouraging the research community to pursue synthetic and/or other studies aimed at the production of michellamine B. In principle, the michellamines can be most efficiently dissected retrosynthetically in two manners (Scheme 1). One retrosynthesis leads to a biomimetic pathway (A) that involves the construction of the naphthalene/isoquinoline bonds *prior* to the formation of the central naphthalene/naphthalene axis. By contrast, the complementary pathway (B) would have the central axis established first, with the two isoquinoline moieties being added subsequently.

The first synthesis of the michellamines was achieved in 1994 following the biomimetic concept.[7,9,10] In this approach, the monomeric halves of the michellamines, korupensamines A (**2**, R = H, X = H, axis, *P*-configured) and B (**3**, R = H, Y = H, axis, *M*-configured), which also occur in *A. korupensis*,[11] were synthesized[9,10] and then homo- or cross-coupled by biomimetic oxidative dimerization of appropriately protected **2** and/or **3** using silver(I) oxide.[7,10]

Scheme 2



The second synthesis,[12] which was completed only a few months later, follows the complementary pathway (B), by first establishing the central bond to result in a dimeric naphthalene unit, which is then connected with the corresponding isoquinoline parts by a double Suzuki-type cross-coupling reaction.

Since then, additional syntheses have been published from the laboratories of Hoye[13] and Dawson[14] following pathway A, the central axis again being built up by oxidative dimerization using Ag_2O[13] or by Suzuki-type cross-couplings.[14] These and other[15−17] synthetic efforts to build up both mono- and dimeric naphthylisoquinoline alkaloids strongly underline the worldwide interest in this promising field of research.

We originally reported the present synthesis in a brief communication in 1994.[12] We now provide greater detail and experimental procedures and also describe some of the ancillary studies that facilitated the synthesis's achievement.

Results and Discussion

The first stage of the synthesis required the preparation of the binaphthalene synthon **5**. To that end, we undertook the synthesis of bromonaphthoquinone **11** since dimerization of **11**, or derivatives thereof, would afford access to the carbon skeleton of **5**.

Brassard[18] reported that chloronaphthoquinone **8** can be prepared regioselectively in 74% overall yield from the known diene **6**[18,19] and 2,6-dichloro-1,4-benzoquinone (**7**) by a Diels−Alder reaction followed by aromatization of the adduct on silica gel and final O-methylation (Scheme 2).

Since bromides are generally more reactive than chlorides in metal-catalyzed coupling reactions, the bromo analogue **11** was prepared from **9**. Using 2,6-dibromo-1,4-benzoquinone (**9**)[20] as the dienophile and **6**[18,19] as diene, bromoquinone **10** was synthesized in 70%

(8) Anon. *J. Nat. Prod.* **1992**, *55*, 1018.
(9) Bringmann, G.; Götz, R.; Keller, P. A.; Walter, R.; Henschel, P.; Schäffer, M.; Stäblein, M.; Kelly, T. R.; Boyd, M. R. *Heterocycles* **1994**, *39*, 503.
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(13) Hoye, T. R.; Chen, M.; Mi, L.; Priest, O. P. *Tetrahedron Lett.* **1994**, *35*, 8747.
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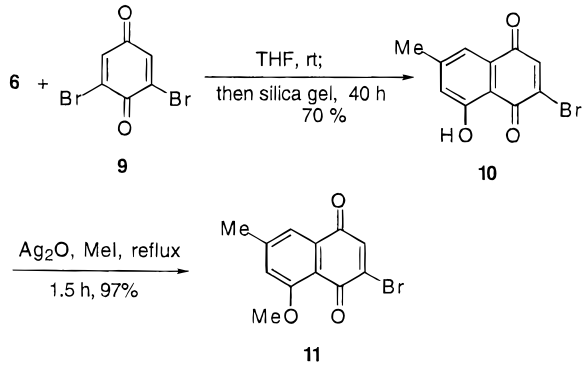
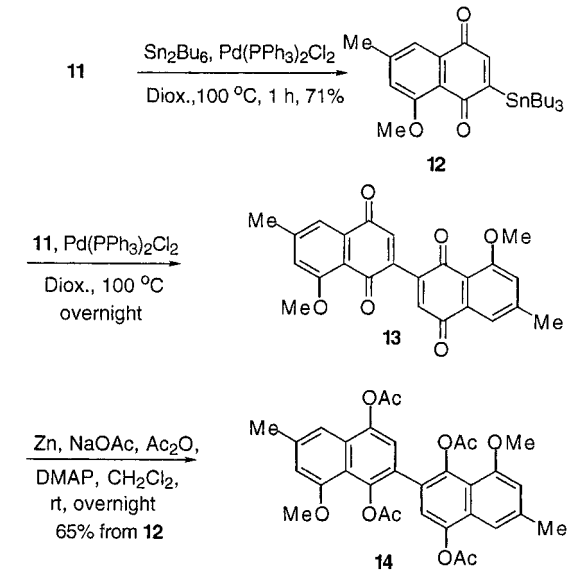
(15) (a) Hoye, T. R.; Mi, L. *Tetrahedron Lett.* **1996**, *37*, 3097. (b) Hoye, T. R.; Chen, M.; *Tetrahedron Lett.* **1996**, *37*, 3099.
(16) Upender, V.; Pollart, D. J.; Liu, J.; Hobbs, P. D.; Olsen, C.; Chao, W.; Bowden, B.; Crase, J. L.; Thomas, D. W.; Pandey, A.; Lawson, J. A.; Dawson, M. I. *J. Heterocyc. Chem.* **1996**, *33*, 1371.
(17) (a) Rama Rao, A. V.; Gurjar, M. K.; Ramana, D. V.; Cheda, A. K. *Heterocycles* **1995**, *43*, 1. (b) Gable, R. W.; Martin, R. L.; Rizzacasa, M. A. *Aust. J. Chem.* **1995**, *48*, 2013. (c) Watanabe, T.; Kamikawa, K.; Uemura, M. *Tetrahedron Lett.* **1995**, *36*, 6695.
(18) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455.
(19) Casey, C. P.; Jones, C. R.; Tukeda, H. *J. Org. Chem.* **1981**, *46*, 2089.

Scheme 3



Scheme 4

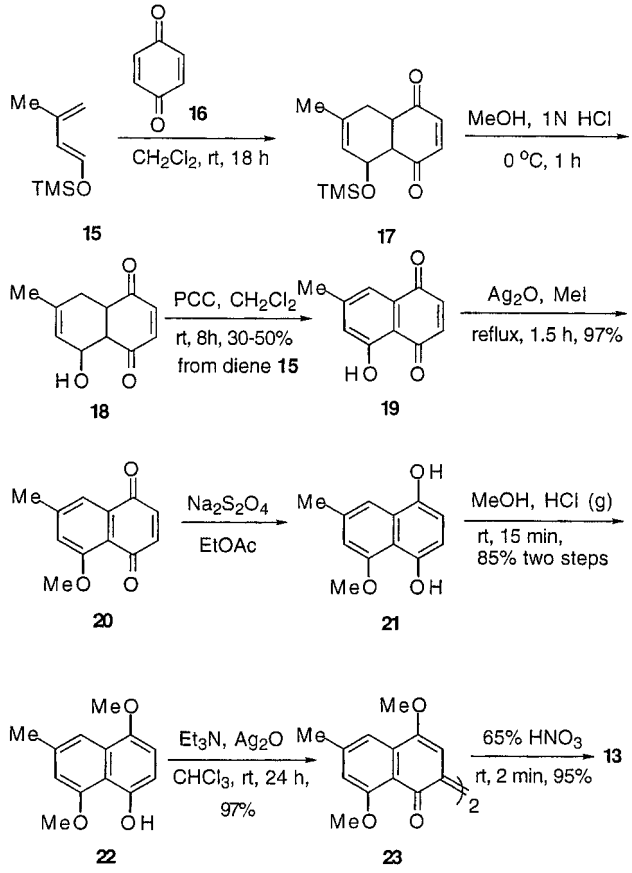


yield (Scheme 3). Methylation of **10** by refluxing in methyl iodide in the presence of silver (I) oxide gave the desired methyl ether **11** in 97% yield.

Bromoquinone **11** was converted into stannane derivative **12** in 71% yield by heating at 100 °C in dioxane with Bu_6Sn_2 and bis(triphenylphosphine)palladium(II) chloride.[21] A second palladium-promoted reaction,[21] utilizing the same catalyst, coupled stannane **12** and bromoquinone **11** to afford binaphthoquinone **13**. Because **13** is light sensitive, it was usually converted without purification to **14** by reductive acetylation. The yield of **14** from **12** is 65% (Scheme 4).

Since the two consecutive coupling reactions leading to **13** use the same reaction conditions, it proved possible to make **13** in a single step. Thus, when half an equivalent of Bu_6Sn_2 was used in the reaction of **11**, after reductive peracetylation, tetraacetate **14** was isolated in 40% yield. We previously reported[12] that the dimerization of **11** to **13** could be realized in a similar yield (43%) by an Ullmann coupling reaction with copper bronze in the presence of tetrakis(triphenylphosphine)palladium-(0) in DMF,[22] but the current Stille-type[23] coupling route is preferred (Scheme 4).

Scheme 5



The binaphthoquinone **13** had been synthesized before by Laatsch[24,25] via an oxidative coupling as shown in Scheme 5. Although our four-step synthesis of **13** is several steps shorter than the one in Scheme 5, we also explored the possibility of improving the latter route. To that end, we first developed an improved synthesis of **19**.[24−26] The new synthesis starts with the Diels−Alder reaction between diene **6**[18,19] and benzoquinone (**16**), which affords the adduct **24** cleanly. Desilylation of **24** in methanol with aqueous HCl and subsequent aromatization gave the desired product **19** in 41% overall yield. When excess benzoquinone (**16**) was used in the Diels−Alder reaction, the leftover **16** could serve as the oxidant for the aromatization, which avoided the use of PCC in the original procedure.

We were pleased with this modified synthesis because it was shorter than the literature sequence, but it was not a perfect solution. For although the Diels−Alder reaction was fast and clean, the cleavage of ketal **24** only afforded naphthoquinone **19** in a moderate yield. And an O-methylation step was still needed for the preparation of **20**.

(20) Prepared in 52% yield using the procedure of Hodgson, H. H.; Nixon, J. *J. Chem. Soc.* **1930**, 1085. The crude product was purified by passing a CH_2Cl_2 solution of it through a column of silica gel. A number of preparations of **9** have been reported in the literature, but we found this method (the oxidation of 2,4,6-tribromophenol using 90% fuming nitric acid) to be the most reliable one.

(21) For recent reviews, see: (a) Farina, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12 (Hegedus, L. S., Ed.), p 161. (b) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3 (Pattenden, G., Ed.), Chapter 2.3. (c) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977.

(22) Shimizu, N.; Kitamura, T.; Watanabe, K.; Yamaguchi, T.; Shigyo, H.; Ohta, T. *Tetrahedron Lett.* **1993**, *34*, 3421.

(23) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

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(25) (a) Krohn, K. *Tetrahedron Lett.* **1980**, *21*, 3557. (b) Krohn, K.; Broser, E. *J. Org. Chem.* **1984**, *49*, 3766.

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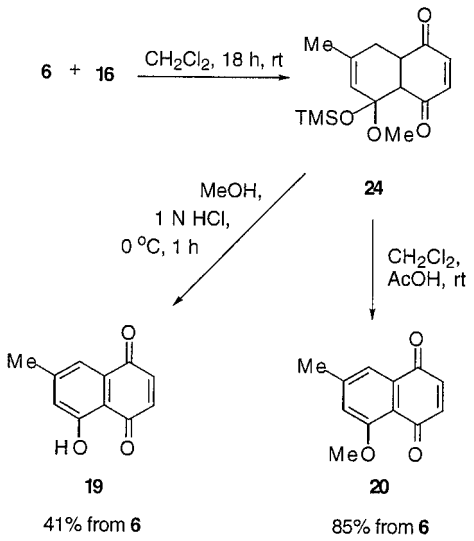
Scheme 6



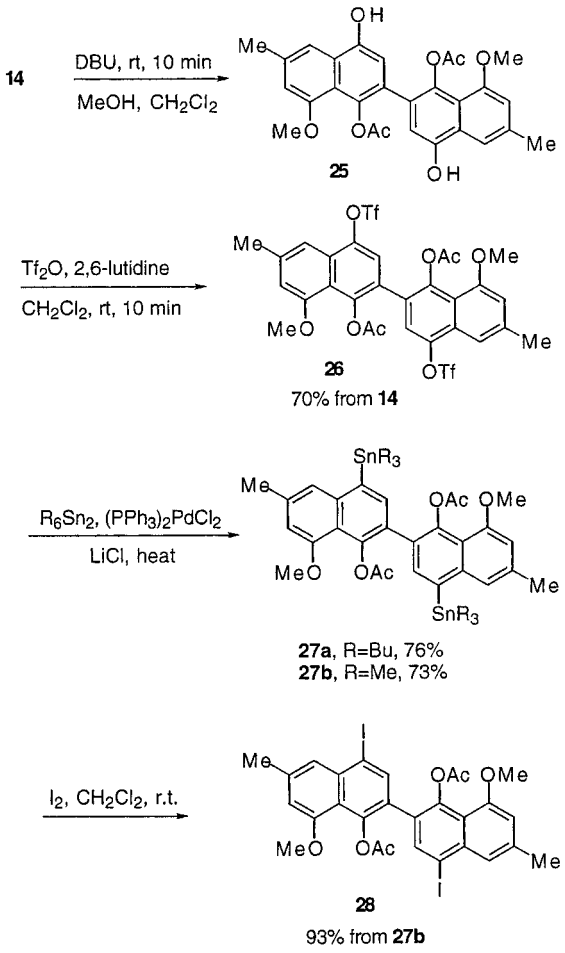
To further improve the synthesis, we sought to optimize the cleavage of ketal **24**. Since an acid milder than HCl might give a cleaner reaction, acetic acid was tested and the result was most rewarding. Thus, after the Diels−Alder reaction between diene **6** and benzoquinone (**16**) in CH_2Cl_2 was complete, acetic acid was added to the reaction solution. Evaporation of the solvent gave, surprisingly, the desired methyl ether **20** instead of the expected phenol **19** as the product (Scheme 6). The reason why **20** is formed instead of **19** is unclear, but the one-pot reaction provides **20** in 85% overall yield based on diene **6**.

Compound **20** was then converted to **13** using the previously reported[24] procedures (Scheme 5). The synthesis of **13** via **20** still has more steps than the route via **11**, but the synthesis of **13**/**14** via **20** is easier and faster, and better suited for large-scale production.

As already mentioned, quinone dimer **13** is light sensitive, so it was usually not purified but instead reductively peracetylated[27] directly to afford tetraacetate **14**. The transformation is conveniently carried out at room temperature by stirring a mixture of crude **13**, zinc powder, acetic anhydride, sodium acetate, and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 overnight. The conversion of **13** to **14** proceeds cleanly: With a pure sample of **13**, **14** was obtained in 95% yield.

Tetraacetate **14** contains the entire carbon skeleton of the binaphthalene synthon **5**, but it is not properly functionalized for biaryl coupling with the isoquinoline units. Refunctionalization began with a selective bisdeacetylation at the less hindered sites with DBU in methanol[28] to give diacetate **25**; without purification, **25** was subsequently converted[29] into ditriflate **26** using trifluoromethanesulfonic anhydride (Tf_2O) and 2,6-lutidine in CH_2Cl_2. The two-step sequence gave **26** in 70% yield from **14** (Scheme 7). Ditriflate **26** was also converted into the distannanes **27a** and **27b** and diiodide[30]

Scheme 7



28 (Scheme 7) so that three different types of binaphthalene units were available for coupling with various isoquinoline synthons.

We anticipated steric hindrance[31] to be the major obstacle in the coupling reaction between the naphthalene and isoquinoline units to give the michellamine skeleton. The isoquinoline unit **4** can be considered a benzene ring with two substituents ortho to the coupling position, while naphthalene **5 (= 26**−**28)** can be regarded as a benzene ring with one substituent ortho to the coupling position. It is very congested at the coupling positions. For elaboration of the best coupling conditions, we decided to carry out model coupling studies in order to save the precious enantiomerically pure isoquinoline unit **34**.

Orcinol derivatives **29, 30,** and **31** were used as models because they are similar to the isoquinoline unit in both steric and electronic respects. The stannane derivatives **30** were prepared[30] by first lithiation of the corresponding bromide **29** followed by reacting with Bu_3SnCl (Scheme 8). The boronic acids[32] **31** were prepared by lithiation of **29** and subsequent reaction with triisopropyl borate as shown in Scheme 8. After various permutations of potential coupling partners were examined (**26**−**28** with

(27) For a leading reference, see: Ulrich, H.; Richter, R. In *Methoden de Organische Chemie (Houben-Weyl)*: *Chinone*; Georg Thieme Verlag: Stuttgart, 1977; Teil I, p 652.

(28) Baptistella, L. H. B.; dos Santos, J. F.; Ballabio, K. C.; Marsaioli, A. J. *Synthesis* **1989**, 436.

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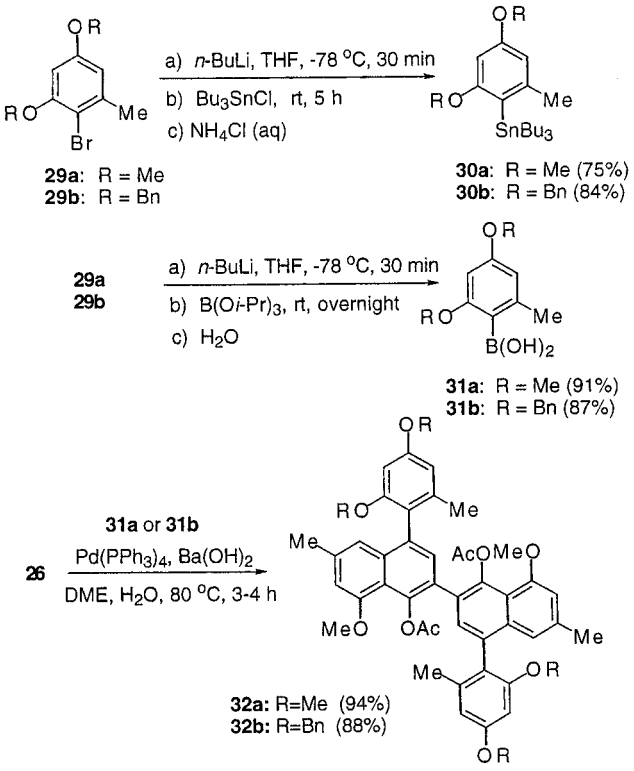
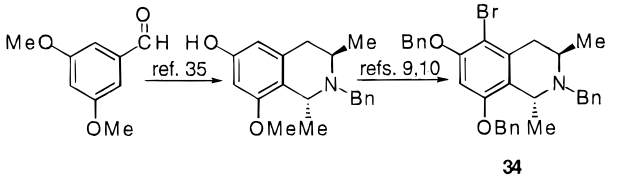
(32) For a leading reference, see: Hevesi, L. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 2 (Ley, S. V., Ed.), p 899.

Scheme 8



Scheme 9

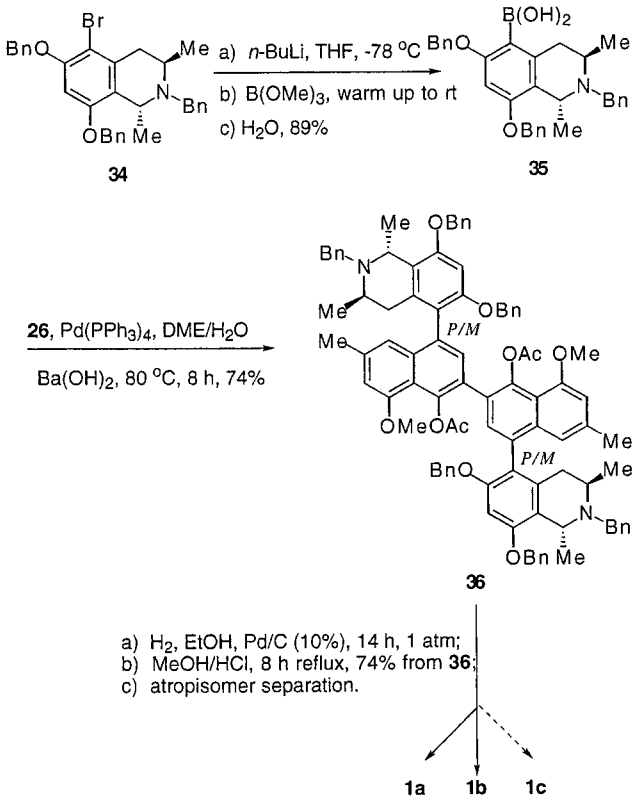


29−**31**), it was determined that Suzuki-type[33,34] cross-coupling reactions between ditriflate **26** and boronic acids **31** gave the best yield for the desired coupling. Coupling reactions between ditriflate **26** and boronic acids **31** were carried out in the presence of tetrakis(triphenylphosphine)palladium(0) and barium hydroxide[34] to afford **32a** and **32b** in 88% and 94% yields, respectively.

With a method established for making the final biaryl bonds, we turned to the synthesis of the michellamines themselves. Preparation of the specifically protected key heterocyclic building block **34** (Scheme 9) in a stereochemically homogeneous form, was done as described previously.[9,10,35]

The subsequent conversion of **34** into the isoquinoline boronic acid **35** was achieved in 89% yield by the same method used above for preparation of the orcinol-derived boronic acids **31** (Scheme 10). Boronic acid **35** was then coupled with ditriflate **26** under the same conditions elaborated for the model compounds to give **36** as a mixture of atropisomers. Deprotection of the benzyl groups was carried out by catalytic hydrogenation; all six benzyl protecting groups were removed by hydrogenation with 10% palladium on charcoal in ethanol at atmo-

Scheme 10



spheric pressure for 14 h. The two acetates in the naphthalene unit were finally taken off in the last step of the synthesis using methanolic HCl.

The resulting mixture of atropisomers was separated by preparative HPLC to give michellamine A (**1a**) and michellamine B (**1b**) (**1a**: **1b** = 1:2.5). The synthetic **1a** and **1b** were shown to be identical, by direct comparison, to authentic, naturally derived materials. However, we were unable to detect any michellamine C (**1c**) in the synthetic mixture even though we had a sample of **1c** as a TLC/HPLC standard. The question of why **1c** is not detectable in either the natural source or our synthetic mixture is intriguing. Atropisomer **1c** is a stable compound[3] (although slightly underrepresented in a thermodynamically dictated mixture of **1a**, **1b**, and **1c**) and has been synthesized previously.[10] While its absence in plant material presumably has to do with the high specificity of the dimerization enzyme, which has recently been isolated,[36] at least one of the two coupling steps in our synthesis must proceed with a high diastereoselectivity. Of great interest would be the axial configuration of the intermediate monocoupled product, which would indicate the degree of asymmetric induction by the stereocenters present in **35** and would thus allow an estimation of the additional degree of asymmetric induction exerted by the first-generated biaryl axis on the second coupling step. Regretably, all attempts to isolate or at least detect such a monocoupled intermediate in the reaction of **35** and **26** failed.

Biological Evaluation of Synthetic 1a/1b. The antiviral activity of the synthetic michellamines was indistinguishable from that previously reported[2,3] for the natural compounds (data not shown).

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(34) (a) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207. (b) Suzuki, A. *Pure Appl. Chem.* **1994**, 213.

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Conclusion. The convergent synthesis described herein provides the michellamines in an overall yield of 24.6% from diene **6**.

Experimental Section[37]

2-Bromo-8-hydroxy-6-methyl-1,4-naphthoquinone (10). To a solution of 2,6-dibromobenzoquinone[20] (**9**) (11.65 g, 43.8 mmol) in 70 mL of dry THF at 0 °C under a nitrogen atmosphere was added dropwise via a syringe pump over 1 h a solution of diene **6** (9.07 g, 48.7 mmol) in 40 mL of dry THF. The resulting solution was stirred at room temperature for 3 h. Then 250 g of 230−400 mesh silica gel was added, and the mixture was shaken until it appeared homogeneous and allowed to stand at room temperature for 48 h. Subsequently, the reaction mixture was put directly onto a silica gel column (4 in. x 10 in.) and purified by eluting with petroleum ether/ethyl acetate (7:3) to give 8.18 g (70%) of bromoquinone **10** as an orange red solid, mp 186−187 °C: IR (KBr) ν 3438, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.45 (3H, s), 7.10 (1H, s), 7.45 (1H, s), 7.46 (1H, s), 11.69 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9, 112.6, 122.0, 125.0, 132.1, 140.2, 141.6, 150.0, 163.0, 182.6, 182.9. Anal. Calcd for $C_{11}H_7O_3Br$: C, 49.47; H, 2.64. Found: C, 49.40; H, 2.57. In addition, 1.27 g (10%) of methyl ether **11** was obtained as a yellow solid.

2-Bromo-8-methoxy-6-methyl-1,4-naphthoquinone (11). A mixture of 5.38 g of **10** (20 mmol), 6.98 g of Ag_2O powder, and 100 mL of iodomethane was refluxed for 1 h. Then the mixture was filtered through Celite and the Celite and the solid were washed with CH_2Cl_2. The filtrate and the wash were combined and evaporated to give 5.49 g (97%) of bromonaphthoquinone **11** as a yellow solid. The crude product was used in the next reaction without further purification. An analytical sample of **11** was obtained by recrystallization from ethanol as a yellow solid, mp 175−177 °C: IR (CH_2Cl_2) ν 1667, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.48 (3H, s), 4.00 (3H, s), 7.10 (1H, s), 7.41 (1H, s), 7.54 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0, 57.1, 117.1, 119.2, 121.1, 134.4, 138.8, 143.5, 147.9, 161.3, 176.5, 183.5; HRMS calcd for $C_{12}H_9BrO_3$ 279.9735, found: 279.9767. Anal. Calcd for $C_{12}H_9BrO_3$: C, 51.27; H, 3.23. Found: C, 51.17; H, 3.15.

2-(Tributylstannyl)-8-methoxy-6-methyl-1,4-naphthoquinone (12). A solution of bromonaphthoquinone **11** (370 mg, 1.31 mmol), hexabutylditin (0.730 mL, 1.45 mmol), and bis(triphenylphosphine)palladium(II) chloride (Aldrich, 138 mg, 15 mol %) in 25 mL of anhydrous dioxane was heated at reflux under a nitrogen atmosphere for 1 h. After cooling, the solution was evaporated under vacuum to yield a brown oil which was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 7:3) to afford **12** as a yellow oil (495 mg, 71%): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (9H, t, J = 7.2 Hz), 1.10 (6H, t, J = 7.2 Hz), 1.28−1.36 (6H, m), 1.48−1.51 (6H, m), 2.47 (3H, s), 3.99 (3H, s), 7.07 (1H, s), 7.10 (1H, s), 7.53 (1H, s). Stannane **12** was converted to **13** and **14** without further characterization.

5-Methoxy-7-methyl-1,4-naphthoquinone (20). To a solution of diene **6**[18,19] (2.37 g, 12.7 mmol) in 100 mL of CH_2Cl_2 under an argon atmosphere at room temperature was added solid benzoquinone **16** (2.61 g, 24.0 mmol) over 5 min. The resulting dark greenish solution was stirred at room temperature for 18 h. An aliquot of the solution was evaporated to dryness and analyzed by NMR spectroscopy, which showed the formation of the Diels−Alder adduct **24**. **24**: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.20 (9H, s), 1.79 (3H, s), 2.01 (1H, dd, J = 5.7, 12.8 Hz), 2.85 (1H, d, J = 12.8 Hz), 3.04 (3H, s), 3.12 (1H, d, J = 5.7 Hz), 3.23 (1H, m), 5.53 (1H, s), 6.62 (1H, d, J = 8.4 Hz), 6.74 (1H, d, J = 8.4 Hz). Then 1.5 mL of acetic acid was added to the reaction mixture and the solvent was evaporated to dryness at room temperature under reduced pressure overnight. A dark, greenish-yellow solid was formed. The solid was mixed with 100 mL of MeOH, and a yellow solid was observed at the bottom of the flask. The solvent was evaporated to dryness and the residue purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3:2) to afford 2.18 g (85%) of **20** as a yellow solid, mp 164−166 °C (lit.[24] mp 166 °C).

2,2′-Bis(1,4-diacetoxy-8-methoxy-6-methylnaphthalene) (14). (A) From Coupling of 11 and 12. In a sealed tube covered with aluminum foil (**13** is light sensitive), a solution of **11** (210 mg, 0.76 mmol), tributylstannane **12** (373 mg, 0.76 mmol), and $(PPh_3)_2PdCl_2$ (80 mg, 15 mol %) in 10 mL of anhydrous dioxane was heated under argon at 110 °C overnight. After cooling, the mixture was poured onto a stirred mixture of Zn dust (497 mg, 7.60 mmol), 4-(dimethylamino)pyridine (371 mg, 3.04 mmol), NaOAc (623 mg, 7.60 mmol), and Ac_2O (2 mL) in 35 mL of CH_2Cl_2, and the new reaction mixture was stirred in the dark overnight. For the workup, the solution was first filtered through Celite, washed with H_2O (3 × 25 mL), dried over Na_2SO_4, and concentrated under vacuum to afford, after chromatography (petroleum ether/ethyl acetate = 1:1), tetraacetate **14** as a light brown oil (283 mg, 65%).

(B) From Dimerization of 11. In a sealable tube covered with aluminum foil, bromoquinone **11** (438 mg, 1.56 mmol), Sn_2Bu_6 (0.39 mL, 0.78 mmol), and $(PPh_3)_2PdCl_2$ (164 mg, 15% mol) were dissolved in 15 mL of anhydrous dioxane under argon. The tube was sealed and heated at 110 °C for 24 h. After being cooled to room temperature, the mixture was poured onto a stirred mixture of Zn dust (1.02 g, 15.6 mmol), 4-(dimethylamino)pyridine (762 mg, 6.24 mmol), NaOAc (1.28 g, 15.6 mmol), and Ac_2O (3 mL) in 50 mL of CH_2Cl_2, and the new reaction mixture was stirred in the dark at room temperature for 15 h. For the workup, the solution was filtered through Celite, washed with H_2O, dried over Na_2SO_4, and concentrated under vacuum. Flash column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1) afforded **14** (178 mg, 40%) as a light brown oil.

(C) From Pure 13. A mixture of binaphthoquinone **13** (2.01 g, 5.00 mmol), dichloromethane (200 mL), zinc dust (10 g), sodium acetate (10 g), acetic anhydride (10 mL), and DMAP (6 g) was stirred in the dark at room temperature for 20 h. Then the mixture was filtered through Celite and the solids were washed with dichloromethane (100 mL). The filtrate and wash were combined and evaporated at reduced pressure and elevated temperature (up to 80 °C) to get rid of the acetic anhydride. The crude product was filtered through a short column of silica gel using dichloromethane as eluent. The filtrate was evaporated to dryness, giving 2.72 g (95%) of **14** as an off-white solid, which was

(37) For general procedures and protocols, see: (a) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4633. (b) Reference 10.

sufficiently pure for carrying out the next step without further purification.

Crystallization of partially purified **14** from CH_2Cl_2/hexanes gave **14** as a white solid, mp 228−230 °C: IR (CH_2Cl_2) ν 1759 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.10 (6H, br s), 2.44 (6H, s), 2.49 (6H, s), 3.89 (6H, s), 6.73 (2H, s), 7.11 (2H, br s), 7.22 (2H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 21.7, 23.0, 56.8, 110.0, 113.7, 119.3, 121.3, 122.5, 126.7, 130.4, 138.2, 142.2, 143.7, 156.4, 169.9; HRMS calcd for $C_{32}H_{30}O_{10}$ 574.1839, found 574.1820. Anal. Calcd for $C_{32}H_{30}O_{10}$: C, 66.89; H, 5.26. Found: C, 66.54; H, 5.20.

2,2′-Bis((1-acetoxy-8-methoxy-6-methyl-4-trifluoromethanesulfonyl)oxy)naphthalene) (26). To a solution of tetraacetate **14** (2.80 g, 4.90 mmol) in 65 mL of CH_2Cl_2 and 65 mL of MeOH was added 1,8-diazabicyclo-[5.4.0]undec-7-ene (3.50 mL, 23.4 mmol) at room temperature. After 15 min, the solvent was evaporated at reduced pressure and 50 mL of water was added to the mixture. The mixture was then extracted with CH_2Cl_2, and the organic layer was separated and dried over Na_2SO_4. Evaporation of the solvent gave crude diacetate **25** which was used without purification in the next reaction. The crude **25** was dissolved in 80 mL of CH_2Cl_2 at 0 °C, 2,6-lutidine (1.0 mL, 8.5 mmol) was added, and then trifluoromethanesulfonic anhydride (1.26 mL, 7.50 mmol) was added dropwise over 3 min. The reaction mixture was stirred at room temperature for 10 min. The solvent was evaporated under vacuum, and the resulting oil was purified by flash column chromatography on silica gel (CH_2Cl_2) to give 2.55 g (70% from **14**) of **26** as a white solid. An analytical sample of **26** was obtained by recrystallization from CH_2Cl_2/hexane as white flakes, mp 190−191 °C: IR (CH_2Cl_2) ν 1766, 1421, 1205 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.07 (6H, br s), 2.56 (6H, s), 3.93 (6H, s), 6.83 (2H, s), 7.40 (2H, br s), 7.48 (2H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 23.1, 56.9, 110.9, 113.4, 119.4 (q, J = 320 Hz) 119.6, 120.7, 121.9, 125.9, 130.3, 140.5, 142.7, 144.7, 156.3; HRMS calcd for $C_{30}H_{24}S_2O_{12}F_6$ 754.0613, found 754.0608. Anal. Calcd for $C_{30}H_{24}S_2O_{12}F_6$: C, 47.75; H, 3.21. Found: C, 47.66; H, 3.18.

(1*R*,3*R*)-*N*-Benzyl-6,7-bis(benzyloxy)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline-5-boronic Acid (35). A solution of 120 mg (0.22 mmol) of bromoisoquinoline **34**[9,10,35] in 10 mL of dry THF under argon was cooled to −78 °C. Over the course of 10 min, 0.16 mL (0.24 mmol) of a 1.5 M solution of *n*-BuLi in hexanes was added and the reaction mixture was stirred 50 min, resulting in an orange solution. Freshly distilled (from sodium) trimethyl borate (0.12 mL, 1.11 mmol) was added, and the reaction mixture was allowed to warm to room temperature overnight. Ten milliliters of water was added, and the mixture was extracted five times with 10-mL portions of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and evaporated under vacuum. The residue was chromatographed on deactivated (7.5% NH_3)[37b] silica gel using 4:1 petroleum ether/ethyl acetate to give, after recrystallization from ethanol/petroleum ether, 100 mg (89%) of boronic acid **35** as a colorless solid, mp 106−108 °C: $[\alpha]^{23}_D$ = +49.3 (c = 1.5 in MeOH); IR (KBr) ν 3600−3100, 3010, 2920, 2910, 2840 cm^{-1}; ^1H NMR ($CDCl_3$, 200.1 MHz) δ 1.30 (3H, d, J = 6.6 Hz), 1.35 (3H, d, J = 6.7 Hz), 2.79 (1H, dd, J = 18.0, 11.3 Hz), 3.13 (1H, dd, J = 18.0, 4.6 Hz), 3.33 (1H, d, J = 14.1 Hz), 3.45−3.56 (1H, m), 3.85 (1H, d, J = 14.1 Hz), 4.08 (1H, q, J = 6.7 Hz), 5.02 (2H, s), 5.04 (2H, s), 5.92 (2H, s), 6.42 (1H, s), 7.19−7.31 (15H, m). Anal. Calcd for $C_{32}H_{34}BNO_4$ (HBr salt): C, 65.33; H, 6.00; N, 2.38. Found: C, 64.93; H, 6.02; N, 2.36.

5′,5″-*O*-Diacetyl-*N*,*N*-dibenzyl-6,6‴,8,8‴-tetra-*O*-benzylmichellamine (36). Into a dry Schlenk flask were placed under argon 60.0 mg (0.11 mmol) of isoquinolineboronic acid **35**, 37.8 mg (0.050 mmol) of ditriflate **26**, 6.0 mg (0.003 mmol) of tetrakistriphenylphosphinepalladium(0), 29.0 mg (0.16 mmol) of barium hydroxide, 3 mL of dimethoxyethane, and 1.5 mL of degassed water. The reaction was heated at 80 °C for 8 h and cooled to room temperature, and volatiles were removed under vacuum. The residue was subjected to preparative thin-layer chromatography on deactivated[37b] silica gel plates using a 2:1 mixture of petroleum ether/ethyl acetate as eluent to give 51.0 mg (74%) of **35** in the form of a light brown solid. Evaluation of the ^1H NMR spectrum is not worthwhile due to substantial peak broadening (due to hindered rotation) and overlap: IR (KBr, HBr salt) ν 3500−3200, 2940, 2900, 1700, 1650, 1570 cm^{-1}. Anal. Calcd for $C_{92}H_{88}N_2O_{10}$ (HBr salt): C, 79.97; H, 6.42; N, 2.03. Found: C, 79.34; H, 6.44; N, 2.16.

Michellamines A (1a) and B (1b). The mixture **36** (50 mg) was dissolved in 2 mL of absolute ethanol and hydrogenated over 5.0 mg of 10% Pd/C for 14 h at room temperature and 1 atm of hydrogen. Catalyst was removed by filtration through a short pad of silica gel, and the filtrate was heated at reflux for 8 h in MeOH that had been saturated in the cold with gaseous HCl. After evaporation of the filtrate, the residue was taken up in MeOH and chromatographed on LH-20 Sephadex, eluting with MeOH. The fractions containing mixtures of **1a** and **1b** were combined and evaporated. The two atropoisomers were separated on an HPLC equipped with a 254 mm detector, using a 2.1 × 25 cm Rainin Dynamax amine phase column. The crude **1a**/**1b** mixture was dissolved in 7 mL of 87:13 chloroform/methanol, and 0.25-mL aliquots were injected and eluted with the same solvent mixture at a flow rate of 12 mL/min to give a total of 6.6 mg (21%) of michellamine A (**1a**) and 16.5 mg (53%) of michellamine B (**1b**) which were identical with authentic samples of naturally derived **1a** and **1b**.

1a: $[\alpha]^{23}_D$ = −8.3 (c = 0.4 in MeOH) (lit.[2] −10.5, c = 0.83 in MeOH); CD $\Delta\epsilon_{209}$ −98.3, $\Delta\epsilon_{242}$ +24.6, $\Delta\epsilon_{258}$ +17.4; IR (KBr, diacetate) ν 3550−3100, 2960, 2910, 1690, 1600 cm^{-1}; ^1H NMR (d_4-MeOH, 500.1 MHz) δ 1.21 (6H, d, J = 6.5 Hz), 1.63 (6H, d, J = 6.5 Hz), 2.12 (2H, m), 2.34 (6H, s), 2.81 (2H, m) 3.64 (2H, m), 4.10 (6H, s), 4.74 (2H, q, J = 6.5 Hz), 6.43 (2H, s), 6.75 (2H, s), 6.85 (2H, s), 7.30 (2H, s); ^{13}C NMR (d_4-MeOH, 125.0 MHz) δ 18.4, 19.3, 22.1, 33.1, 45.1, 49.4, 57.0, 102.0, 108.0, 113.1, 115.2, 119.1, 120.4, 124.2, 133.1, 134.7, 136.7, 137.5, 152.2, 155.5, 156.9, 159.1.

1b: $[\alpha]^{23}_D$ = −16.2 (c = 0.72 in MeOH) (lit.[2] −14.8, c = 0.74 in MeOH); CD $\Delta\epsilon_{209}$ −53.8, $\Delta\epsilon_{214}$ −53.8; IR (KBr, HBr salt) ν 3600−3150, 2960, 2910, 1600 cm^{-1}; ^1H NMR (d_4-MeOH, 500.1 MHz) δ 1.16 (3H, d, J = 6.0 Hz), 1.19 (3H, d, J = 6.5 Hz), 1.59 (3H, d, J = 6.5 Hz), 1.63 (6H, d, J = 6.5 Hz), 2.03 (1H, dd, J = 18.5, 11.5 Hz), 2.25 (1H, dd, J = 18.5, 4.5 Hz), 2.33 (3H, s), 2.36 (3H, s), 2.42 (1H, dd, J = 18.5, 11.3 Hz), 2.69 (1H, dd, J = 18.5, 4.0 Hz), 3.48−3.55 (2H, m), 4.09 (3H, s), 4.10 (3H, s), 4.62 (1H, q, J = 6.0 Hz), 4.66 (1H, q, J = 6.0 Hz), 6.41 (2H, s), 6.75 (1H, s), 6.84−6.85 (3H, m), 7.26 (1H, s), 7.30 (1H, s); ^{13}C NMR (d_4-MeOH, 125.0 MHz, diacetate) δ 13.1, 19.1, 20.1, 20.2, 22.1, 22.2, 30.7, 30.7, 33.9, 34.9, 44.5, 44.6, 56.9,

57.0, 101.8, 101.9, 108.3, 114.8, 115.1, 115.2, 118.9, 119.0, 119.2, 119.3, 120.3, 120.4, 124.4, 124.5, 134.6, 134.7, 135.1, 135.2, 136.6, 136.7, 137.4, 137.5, 152.1, 152.2, 155.5, 155.6, 156.3, 156.4, 158.0, 158.1, 180.2, 180.2.

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Supporting Information Available: Experimental details concerning model studies and other compounds (**19**, **27a**, **27b**, **28**, **29b**, **30a**, **30b**, **31a**, and **31b**) not directly related to the final synthetic sequence (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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