Total Synthesis of Nothapodytine B and (−)-Mappicine

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Abstract: Concise total syntheses of naturally occurring nothapodytine B (**1**, mappicine ketone) and (−)-mappicine (**3**) are detailed. The approach is based on the implementation of a room-temperature, inverse electron demand Diels−Alder reaction of the *N*-sulfonyl-1-aza-1,3-butadiene **11** for assemblage of a pyridone D ring precursor central to the structure. A Friedlander condensation is utilized for constructing the AB ring system of **1** and **3**. An acid-catalyzed reaction sequence is used to accomplish a deprotection with subsequent ring-closure for introduction of the C ring in a single step.

Nothapodytine B (**1**) along with nothapodytine A (**2**) have recently been isolated from *Nothapodytes foetida* of which the ethanol extract exhibits significant cytotoxity in the human KB cell line (Figure 1).[1] Nothapodytine B (**1**) is an oxidized derivative of mappicine (**3**)[2] and an E ring decarboxylated analogue of camptothecin (**4**), the parent member of a clinically useful class of DNA topoisomerase I inhibitors that exhibit efficacious antitumor activity.[3] Recently, nothapodytine B (**1**, mappicine ketone) has been identified as an antiviral lead with reported selective activities against HSV-1, HSV-2, and human cytomegalovirus (HCMV) with PR_{50}'s of 2.9, 0.5, and 13.2 μM, respectively.[4] Because the antiviral mechanism of nothapodytine B (**1**) is distinct from that of Acyclovir (ACV) as demonstrated by the observation that ACV-resistant HSV-1 and HSV-2 are inhibited by nothapodytine B (**1**) and that nothapodytine B-resistant mutants remain sensitive to ACV, potentially it may be used with ACV cooperatively.[5] While camptothecin (**4**) is now available from natural sources in quantity, nothapodytine B (**1**) has only been isolated from *Nothapodytes foetida* and in low content which prohibits isolation of useful amounts for further studies. Hence, recent efforts have described improvements in the degradation of camptothecin[6] as well as the development of synthetic routes to nothapodytine B (**1**)[6] and related analogues.[4,6]

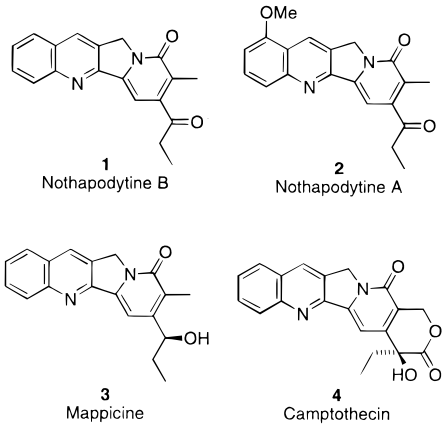

Figure 1.

In conjunction with synthetic efforts on this important class of naturally occurring alkaloids, herein we detail concise total syntheses of nothapodytine B (**1**) and (−)-mappicine (**3**). The availability of the natural products has permitted their cytotoxicity testing addressing ambiguities regarding their contribution to the *Nothapodytes foetida* EtOH extract activity.[1] Central to our approach was the implementation of a room-temperature, inverse electron demand Diels−Alder reaction[7] of the *N*-sulfonyl-1-aza-1,3-butadiene **11** for the introduction of the pyridone D ring[8] with assemblage of the full carbon skeleton of **1** (Scheme 1). The incorporation of a strong C4 electron-withdrawing substituent into the electron-deficient azadiene **11** accelerates its rate of participation in the $LUMO_{diene}$-controlled Diels−Alder reaction to the extent that cycloaddition could be confidently expected to occur at 25 °C without altering the inherent cycloaddition regioselectivity.[9] That is, the substitution of the diene with both a strong C4 and C2 electron-withdrawing group

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(6) From camptothecin: (a) Fortunak, J. M. D.; Mastrocola, A. R.; Mellinger, M.; Wood, J. L. *Tetrahedron Lett.* **1994**, *35*, 5763 and Kingsbury, W. D. *Tetrahedron Lett.* **1988**, *29*, 6847. Total synthesis: (b) Kametani, T.; Takeda, H.; Nemoto, H.; Fukumoto, K. *Heterocycles* **1975**, *3*, 167. Kametani, T.; Takeda, H.; Nemoto, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1825. (c) Comins, D. L.; Saha, J. K. *J. Org. Chem.* **1996**, *61*, 9623. (d) Josien, H.; Curran, D. P. *Tetrahedron* **1997**, *53*, 8881.

(7) Boger, D. L. *Chemtracts: Org. Chem.* **1996**, *9*, 149. Boger, D. L.; Patel, M. In *Progress in Heterocyclic Chem., Vol. 1*; Suschitzky, H., Scriven, E. F. V., Eds.; Pergamon: London, 1989; p 30. Boger, D. L. *Chem. Rev. (Washington, D.C.)* **1986**, *86*, 781. Boger, D. L. *Bull. Soc. Chim. Belg.* **1990**, *99*, 599. Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic: San Diego, CA, 1987. Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.

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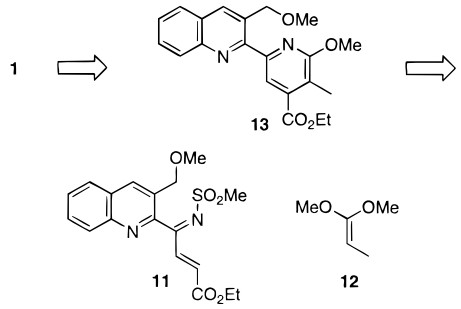
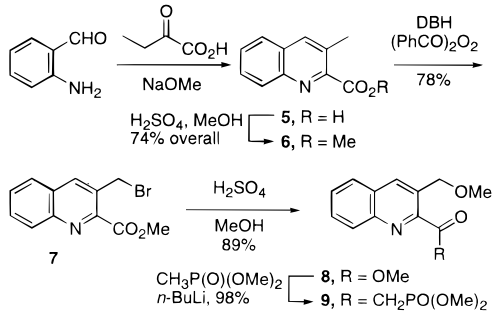
Scheme 1



Scheme 2

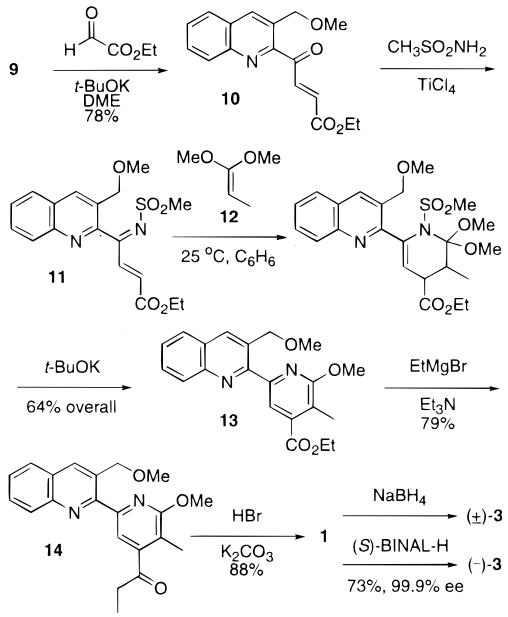


does not diminish or reverse the inherent regioselectivity of the [4 + 2] cycloaddition reaction despite their potential to do so, but both contribute to a reaction rate acceleration by lowering the diene LUMO despite this noncomplementary substitution on the diene.

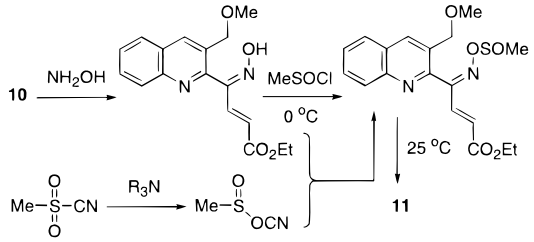
Friedlander condensation of 2-aminobenzaldehyde with 2-oxobutyric acid (NaOMe, MeOH, 65 °C, 12 h) and subsequent Fischer esterification (H_2SO_4, MeOH, 65 °C, 24 h) of the crude carboxylic acid **5** provided methyl 3-methylquinoline-2-carboxylate (**6**) in 70% overall yield as described (Scheme 2).[10] Analogous to a Danishefsky procedure employing NBS/CCl_4, benzylic bromination of **6** with 1,3-dibromo-5,5-dimethylhydantoin (DBH, 0.5 equiv) provided **7** smoothly in high yield (78%) accompanied by ≤10% of the dibromination product in refluxing CCl_4 containing a catalytic amount of benzoyl peroxide (0.05 equiv).[11] Conversion of **7** to the β-ketophosphonate **9** was accomplished following the procedure outlined by Ciufolini.[12] Thus, treatment of **7** with concentrated H_2SO_4 (10 equiv) in MeOH (65 °C, 12 h) provided **8** in excellent yield (89%) and subsequent treatment with α-lithio dimethyl methylphosphonate (2 equiv, −78 °C, 1 h) afforded **9** quantitatively.

Wadsworth−Horner−Emmons reaction of the β-keto phosphonate **9** to provide the α,β-unsaturated γ-keto ester **10**

Scheme 3



Scheme 4



(Scheme 3) was carried out with ethyl glyoxylate and *t*-BuOK in DME (−20 to 25 °C, 5 h), Scheme 3.[13] Two approaches to the conversion of **10** to the key *N*-sulfonyl-1-aza-1,3-butadiene **11** required for use in the $LUMO_{diene}$-controlled Diels−Alder reaction were examined. The initial two-step procedure requiring conversion of **10** to the corresponding oxime[14] (NH_2OH−HCl, EtOH, 25 °C, 24 h, 84−92%) followed by oxime *O*-methanesulfinate formation (CH_3SOCl, Et_3N, CH_2Cl_2, 0 °C, 20 min) and in situ homolytic rearrangement (Scheme 4)[9,15] failed to provide **11** in yields competitive with a direct condensation of **10** with methanesulfonamide. Similarly, treatment of the oxime **10** with methanesulfonyl cyanide under conditions (CCl_4, Et_3N, or DBU) that lead to rearrangement to methylsulfinyl cyanate, subsequent oxime *O*-sulfinate formation, and homolytic rearrangement to the methanesulfonylimine failed to provide **11** cleanly (Scheme 4).[16] By contrast, the direct $TiCl_4$-promoted (1.3 equiv) condensation of **10** with methane-

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(10) Danishefsky, S.; Bryson, T. A.; Puthenpurayil, J. *J. Org. Chem.* **1975**, *40*, 796.

(11) NBS (1.4 equiv) and AIBN (0.14−0.19 equiv), CCl_4 (reflux) provided **7** in lower conversion (45−49%) accompanied by the dibromination product (15−24%), and larger amounts of NBS (2.0 equiv, 0.2 equiv AIBN) provided predominately the dibrominated product (75%). For methyl 3-(dibromomethyl)quinoline-2-carboxylate: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.91 (s, 1H), 8.18 (d, 1H, J = 8.5 Hz), 7.92 (s, 1H), 7.90 (d, 1H, J = 8.2 Hz), 7.77 (ddd, 1H, J = 1.5, 6.9, 8.4 Hz), 7.64 (ddd, 1H, J = 1.1, 6.9, 8.1 Hz), 4.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 146.8, 142.7, 139.8, 135.0, 131.6, 129.9, 129.3, 128.6, 127.8, 53.6, 37.0; IR (film) ν_{max} 3062, 2950, 1721, 1558, 1489, 1455, 1436, 1304, 1195, 1168, 1139, 1070, 853, 786, 753, 694, 618 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 359.9072 (M + H$^+$, $C_{12}H_9Br_2NO_2$ requires 359.9058).

(12) Ciufolini, M. A.; Roschangar, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1692; *Tetrahedron* **1997**, *53*, 11049.

(13) The ratio of trans:cis **10** obtained in the Wadsworth−Horner−Emmons reaction was 4: 1, and this ratio was not altered employing different reaction condition (K_2CO_3, DMF, −25 to 25 °C, 24 h).

(14) For the oxime: ^{1}H NMR ($CDCl_3$, 400 MHz) 1:1 mixture of syn: anti isomers: δ 9.90 (br s, 1H), 8.32 (s, 1H), 8.19 and 7.62 (two d, 1H, J = 16.3 and 16.1 Hz), 8.14 (t, 1H, J = 9.2 Hz), 7.86 (t, 1H, J = 7.8 Hz), 7.72 (t, 1H, J = 7.7 Hz), 7.59 (t, 1H, J = 7.5 Hz), 5.92 and 5.62 (two d, 1H, J = 16.3 and 16.1 Hz), 4.59 and 4.50 (two s, 2H), 4.19 and 4.15 (two q, 2H, J = 7.1 and 7.2 Hz), 3.42 and 3.40 (two s, 3H), 1.24 and 1.21 (two t, 3H, J = 7.1 and 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0, 155.5, 146.9, 146.5, 139.9, 135.1, 130.4, 130.1, 129.9, 129.1, 127.7, 127.6, 125.5, 70.7, 60.7, 58.7, 14.1; IR (film) ν_{max} 2925, 2854, 1714, 1622, 1494, 1448, 1367, 1301, 1260, 1183, 1107, 1035, 974, 760 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 315.1351 (M + H$^+$, $C_{17}H_{18}N_2O_4$ requires 315.1345).

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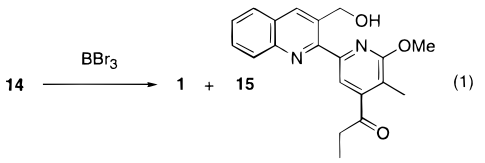
sulfonamide (1.5 equiv, 3 equiv of Et_3N, CH_2Cl_2, −30 to 25 °C, 1 h) cleanly provided **11** (Scheme 3).[8,9,17] This latter one-step procedure afforded **11**[18] in high yield and of a sufficient purity that it could be employed directly in the following Diels−Alder reaction. Treatment of **11** with 1,1-dimethoxy-1-propene **12**[19] at *room temperature* (12 h, C_6H_6) led to the formation of the sensitive [4 + 2] cycloadduct. Notably, the deliberate incorporation of the noncomplementary C4 electron-withdrawing substituent resulted in a Diels−Alder cycloaddition that proceeded at 25 °C presumably by lowering the diene LUMO without altering the inherent [4 + 2] cycloaddition regioselectivity. Due to the expected sensitivity of the Diels−Alder adduct to hydrolysis, subsequent aromatization of the crude adduct (*t*-BuOK, THF, −35 °C, 30 min) to provide **13** was conducted in yields as high as 65% from **10** (3 steps) without intermediate isolations. Presumably, aromatization proceeds by initial base-catalyzed elimination of methanesulfinic acid which is facilitated by the C4−CO_2Me substitution followed by elimination of methanol to provide **13**.[8]

Addition of EtMgBr to **13** in the presence of a tertiary amine[20] (EtMgBr, Et_3N, toluene, −10 °C, 4 h, 79%) proceeded cleanly to give the corresponding ethyl ketone **14** without competitive tertiary alcohol formation by virtue of tertiary amine-promoted ketone enolization. The final conversion of **14** to **1** required deprotection of both the benzylic and pyridone methyl ethers and subsequent cyclization to form the C ring. This was accomplished in one operation by treatment of **14** with a saturated solution of HBr(g) in CF_3CH_2OH (80 °C, 24 h)[8] followed by the addition of K_2CO_3 (25 °C, 1 h) to provide **1** directly without workup and isolation of the intermediate benzylic bromide. This approach worked beautifully to give **1** in 88% overall yield, and the final product proved identical in all respects with the properties reported for authentic material.[1,6] Preliminary efforts involving treatment of **14** with BBr_3 (CH_2Cl_2, −78 to 25 °C, 24 h) were less successful and gave a 1:1 mixture of **1** and benzyl alcohol **15** (eq 1).[18] Prolonged reaction times and elevated temperatures did not change this product ratio suggesting that alcohol **15** was not an intermediate in route to **1** but a competitive side product.



(1)

Reduction of **1** with $NaBH_4$ as first described by Kametani and later by Kingsbury and Comins provided (±)-mappicine (**3**).[6] Additionally, reduction of **1** with (*S*)-BINAL-H[21] provided (*S*)-(−)-mappicine (73%, 99.9% ee) which exhibited a CD spectrum identical with that described for naturally occurring material confirming the original absolute configuration assignment.[2] The enantiomeric purity of the synthetic sample was established by HPLC resolution of the enantiomers on a ChiralCel OD column (α = 1.19) enlisting racemic **3** for comparison. The cytotoxic evaluation (L1210) of **1**, **3**, and related synthetic intermediates revealed that **1** (40 μM), **13** (85 μM), and **14** (>280 μM) were essentially inactive and both (−)-(*S*)-**3**, which to our knowledge has not been reported previously as well as (+)-(*R*)-**3** was also only weakly cytotoxic (IC_{50} = 13 and 23 μM, respectively).

Thus, concise and efficient total syntheses of nothapodytine B (**1**, six steps from **9**,[12] 35% overall; 11 steps from 2-aminobenzaldehyde, 17% overall) and (*S*)-(−)-mappicine (**3**) based on the implemenation of a room temperature [4 + 2] cycloaddition of a *N*-sulfonyl-1-azadiene was accomplished and suggest straightforward extensions to camptothecin and related analogues. These and related efforts are in progress and will be reported in due course.

Experimental Section

Methyl 3-(Bromomethyl)quinoline-2-carboxylate (7). A solution of **6**[10] (2.8 g, 13.9 mmol) in CCl_4 (200 mL) was treated with 1,3-dibromo-5,5-dimethylhydantoin (2.0 g, 6.9 mmol) and benzoyl peroxide (166 mg, 0.7 mmol) and warmed at reflux under N_2 for 5 h. The reaction mixture was filtered through SiO_2 (15% EtOAc−hexane), and the filtrate was concentrated under reduced pressure. Chromatography (SiO_2, 10% EtOAc−hexane) afforded **7** (3.0 g, 78%) as a white solid: R_f 0.4 (25% EtOAc−hexane, dibromide R_f 0.5); mp 85−86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (s, 1H), 8.19 (d, 1H, J = 8.5 Hz), 7.80 (d, 1H, J = 8.1 Hz), 7.75 (ddd, 1H, J = 1.4, 6.9, 8.4 Hz), 7.61 (ddd, 1H, J = 1.1, 7.0, 8.1 Hz), 4.95 (s, 2H), 4.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 147.4, 146.3, 138.6, 130.7, 130.4, 129.8, 128.8, 128.2, 127.2, 53.2, 30.1; IR (film) ν_{max} 2916, 1712, 1454, 1300, 1218, 1199, 1137, 1077, 776, 752 cm^{-1}; FABHRMS (NBA-NaI) *m*/*e* 279.9983 (M + H$^+$, $C_{12}H_{10}BrNO_2$ requires 279.9973).

Anal. Calcd for $C_{12}H_{10}BrNO_2$: C, 51.45; H, 3.60; N, 5.00. Found: C, 51.58; H, 3.48; N, 4.76.

Methyl 3-(Methoxymethyl)quinoline-2-carboxylate (8).[12] A solution of **7** (194 mg, 0.69 mmol) in MeOH (25 mL) was treated cautiously with concentrated H_2SO_4 (682 mg, 6.9 mmol) and warmed at reflux under N_2 for 16 h. After cooling, the reaction mixture was neutralized with the addition of saturated aqueous $NaHCO_3$ (pH = 8) extracted with EtOAc (3 × 50 mL), and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (SiO_2, 40% EtOAc−hexane) afforded **8** (142 mg, 89%) as a white solid: mp 68−69 °C (lit.[12] mp 63−64 °C); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.43 (s, 1H), 8.19 (d, 1H, J = 8.5 Hz), 7.82 (d, 1H, J = 8.1 Hz), 7.71 (ddd, 1H, J = 1.4, 6.9, 8.4 Hz), 7.61 (ddd, 1H, J = 1.0, 8.1, 8.6 Hz), 4.90 (s, 2H), 4.03 (s, 3H), 3.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 146.5, 146.0, 135.3, 131.8, 129.8 (2C), 128.7, 128.4, 127.3, 71.1, 58.7, 52.9; IR (film) ν_{max} 2950, 1725, 1565, 1456, 1299, 1207, 1138, 1111, 1070, 785, 754 cm^{-1}; FABHRMS (NBA-NaI) *m*/*e* 232.0981 (M + H$^+$, $C_{13}H_{13}NO_3$ requires 232.0974).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.21; H, 5.47; N, 6.09.

Dimethyl [2-[3-(Methoxymethyl)quinolin-2-yl]-2-oxoethyl]phosphonate (9).[12] A solution of dimethyl methylphosphonate (1.93 mL, 17.3 mmol) in anhydrous THF (20 mL) under N_2 at −78 °C was treated with *n*-BuLi (1.6 M in hexane, 10.81 mL), and the solution was allowed to stir at −78 °C for 30 min before a solution of **8** (1.0 g, 4.32 mmol) in anhydrous THF (10 mL) was added. The resulting yellow solution was stirred at −78 °C for 1 h and quenched with the addition of saturated aqueous NH_4Cl (10 mL). The reaction mixture was extracted with EtOAc (3 × 30 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (SiO_2, 90%

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(17) Jennings, W. B.; Lovely, C. J. *Tetrahedron Lett.* **1988**, *29*, 3725.
(18) For **11**: ^{1}H NMR ($CDCl_3$, 250 MHz) 1:1 mixture of syn:anti isomers: δ 8.31 and 7.48 (two d, 1H, J = 16 and 16 Hz), 8.26 and 8.17 (two s, 1H), 8.09 and 7.85 (two d, 1H, J = 8.3 and 8.1 Hz), 6.19 and 6.07 (two d, 1H, J = 16 and 16 Hz), 4.65 and 4.60 (two s, 2H), 4.21 (q, 2H, J = 7.1 Hz), 3.43 and 3.39 (two s, 3H), 3.22 and 3.13 (two s, 3H), 1.27 (t, 3H, J = 7.1 Hz); FABMS (NBA-NaI) *m*/*e* 377 (M + H$^+$, $C_{18}H_{20}N_2O_5S$ requires 377). For alcohol **15**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (bs, 1H), 8.15 (bs, 1H), 7.93 (s, 1H), 7.86 (d, 1H, J = 8.0 Hz), 7.74 (t, 1H, J = 7.7 Hz), 7.58 (t, 1H, J = 7.4 Hz), 5.30 (bs, 1H), 4.83 (d, 2H, J = 5.2 Hz), 4.06 (s, 3H), 2.97 (q, 2H, J = 7.1 Hz), 2.28 (s, 3H), 1.23 (t, 3H, J = 7.1 Hz); FABHRMS (NBA-NaI) *m*/*e* 337.1564 (M + H$^+$, $C_{20}H_{20}N_2O_3$ requires 337.1552).
(19) Mueller, F. J.; Eichen, K. German Patent 2331675; *Chem. Abstr.* **1974**, *81*, 63153v.
(20) Kikkawa, I.; Yorifuji, T. *Synthesis* **1980**, 877.
(21) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

EtOAc−hexane) afforded **9** (1.37 g, 98%) as a white solid: mp 46−47 °C (lit.[12] mp 51 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (s, 1H), 7.96 (d, 1H, J = 8.4 Hz), 7.68 (d, 1H, J = 8.1 Hz), 7.58 (ddd, 1H, J = 1.4, 6.9, 8.4 Hz), 7.46 (ddd, 1H, J = 1.2, 7.0, 8.1 Hz), 4.79 (s, 2H), 4.07 (d, 2H, J = 22.1 Hz), 3.61 (d, 6H, J = 11.2 Hz), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.0 (d, J = 7 Hz), 148.7, 145.0, 134.3, 132.3, 129.51, 129.45, 128.9, 128.7, 127.1, 70.8, 58.5, 52.49, 52.45, 36.3 (d, J = 130 Hz); IR (film) ν_{max} 2954, 1696, 1453, 1258, 1191, 1115, 1031, 990, 880, 849, 792, 755 cm^{-1}; FABHRMS (NBA-NaI) *m*/*e* 324.1010 (M + H$^+$, $C_{15}H_{18}NO_5P$ requires 324.1001).

Anal. Calcd for $C_{15}H_{18}NO_5P$: C, 55.73; H, 5.61; N, 4.33. Found: C, 55.68; H, 5.93; N, 4.05.

Ethyl 4-[3-(Methoxymethyl)quinolin-2-yl]-4-oxo-2(*E*)-butenoate (10). Method A. A solution of *t*-BuOK (256 mg, 2.3 mmol) in anhydrous DME (5 mL) at −20 °C was treated with **9** (618 mg, 1.9 mmol) in DME (10 mL) and ethyl glyoxylate (50% in toluene, 0.75 mL, 3.8 mmol) sequentially. The reaction mixture was warmed to 25 °C gradually and stirred at 25 °C for 5 h. The resulting solution was diluted and extracted with EtOAc (2 × 25 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (SiO_2, 10% EtOAc−hexane) afforded **10** (446 mg, 78%) as a white solid (trans:cis = 4:1). Careful chromatography was employed to obtain samples of the pure trans and cis isomers.

Method B. A solution of K_2CO_3 (207 mg, 1.1 mmol) in anhydrous DMF (2 mL) at −20 °C was treated with **9** (227 mg, 0.70 mmol) in DMF (2 mL) and ethyl glyoxylate (50% in toluene, 0.28 mL, 1.4 mmol) sequentially. The reaction mixture was warmed to 25 °C gradually and stirred at 25 °C for 24 h. The resulting solution was diluted and extracted with EtOAc (2 × 25 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (SiO_2, 10% EtOAc−hexane) afforded **10** (137 mg, 65%) as a white solid (trans:cis = 4:1).

***Trans* isomer:** mp 63−64 °C; R_f = 0.50 (SiO_2, 17% EtOAc−hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.60 (d, 1H, J = 15.9 Hz), 8.45 (s, 1H), 8.17 (d, 1H, J = 8.4 Hz), 7.84 (d, 1H, J = 8.0 Hz), 7.74 (ddd, 1H, J = 1.4, 6.8, 8.4 Hz), 7.62 (ddd, 1H, J = 1.2, 6.8, 8.1 Hz), 6.92 (d, 1H, J = 15.9 Hz), 4.96 (s, 2H), 4.23 (q, 2H, J = 7.1 Hz), 3.54 (s, 3H), 1.33 (t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.0, 165.8, 150.0, 145.7, 137.6, 134.8, 132.7, 132.0, 130.1, 129.8, 129.14, 129.10, 127.5, 71.2, 61.2, 58.9, 14.2; IR (film) ν_{max} 2981, 2923, 2817, 1719,1676, 1447, 1336, 1300, 1266, 1228, 1176, 1111, 1100, 990, 909, 776, 747 cm^{-1}; FABHRMS (NBA-NaI) *m*/*e* 300.1242 (M + H$^+$, $C_{17}H_{17}NO_4$ requires 300.1236).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.09; H, 6.10; N, 4.39.

***Cis* isomer:** mp 74−75 °C; R_f = 0.45 (SiO_2, 17% EtOAc−hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.49 (s, 1H), 8.08 (d, 1H, J = 8.1 Hz), 7.85 (d, 1H, J = 8.1 Hz), 7.70 (ddd, 1H, J = 1.5, 6.9, 8.4 Hz), 7.60 (ddd, 1H, J = 1.2, 6.9, 8.1 Hz), 7.43 (d, 1H, J = 12.1 Hz), 6.28 (d, 1H, J = 12.0 Hz), 5.07 (s, 2H), 4.03 (q, 2H, J = 7.2 Hz), 3.60 (s, 3H), 1.16 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.3, 165.7, 150.4, 145.4, 141.5, 134.1, 132.6, 129.8, 129.5, 129.1, 128.7, 127.4, 125.8, 70.7, 60.7, 58.8, 13.7; IR (film) ν_{max} 2982, 2933, 2821, 1714, 1688, 1454, 1382, 1280, 1218, 1159, 1119, 1100, 1029, 949, 784, 755 cm^{-1}; FABHRMS (NBA-NaI) *m*/*e* 300.1246 (M + H$^+$, $C_{17}H_{17}NO_4$ requires 300.1236).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.19; H, 5.79; N, 4.54.

Ethyl 2-[3-(Methoxymethyl)quinolin-2-yl]-6-methoxy-5-methylpyridine-4-carboxylate (13). A solution of **10** (70 mg, 0.23 mmol) and $CH_3SO_2NH_2$ (34 mg, 0.35 mmol) in anhydrous CH_2Cl_2 (8 mL) at −30 °C under N_2 was treated with $TiCl_4$ (1.0 M in CH_2Cl_2, 0.3 mL) and Et_3N (0.11 mL, 0.70 mmol) sequentially and warmed to 25 °C gradually (1 h). After stirring for an additional 1 h at 25 °C, the reaction mixture was filtered through Celite (50% EtOAc−hexane, 1 drop of Et_3N), and the filtrate was concentrated under reduced pressure. A solution of crude *N*-sulfonyl-1-aza-1,3-butadiene **11**[18] (0.23 mmol) and 1,1-dimethoxy-1-propene (**12**,[19] 0.3 mL) in 2 mL of anhydrous C_6H_6 was stirred at 25 °C for 12 h under N_2, and the reaction mixture was concentrated in vacuo. The residue was dissolved in 2.3 mL of anhydrous THF, cooled to −35 °C under N_2, and treated with *t*-BuOK (200 mg, 1.8 mmol). After stirring at −35 °C for 30 min, the reaction mixture was diluted and extracted with EtOAc (2 × 20 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (SiO_2, 7% EtOAc−hexane) afforded **13** (55 mg, 64%; typically 40−65%) as a white solid: mp 80−81 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.42 (s, 1H), 8.14 (d, 1H, J = 8.4 Hz), 8.10 (s, 1H), 7.84 (d, 1H, J = 8.1 Hz), 7.68 (ddd, 1H, J = 1.3, 6.9, 8.3 Hz), 7.52 (ddd, 1H, J = 1.0, 8.0, 8.9 Hz), 5.05 (s, 2H), 4.39 (q, 2H, J = 7.1 Hz), 4.02 (s, 3H), 3.46 (s, 3H), 3.46 (s, 3H), 1.39 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 161.8, 154.4, 152.8, 146.6, 140.5, 134.5, 131.1, 129.3, 129.3, 127.7, 127.4, 126.9, 121.3, 117.0, 72.4, 61.5, 58.6, 54.3, 14.2, 12.7; IR (film) ν_{max} 2978, 1722, 1599, 1567, 1451, 1359, 1236, 1105, 1065, 927 cm^{-1}; FABHRMS (NBA-NaI) *m*/*e* 367.1650 (M + H$^+$, $C_{21}H_{22}N_2O_4$ requires 367.1658).

Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.77; H, 6.25; N, 7.27.

1-[2-[3-(Methoxymethyl)quinolin-2-yl]-6-methoxy-5-methylpyridin-4-yl]propan-1-one (14). A solution of **13** (27.4 mg, 0.08 mmol) in anhydrous toluene (2.8 mL) under N_2 was treated with Et_3N (0.13 mL, 0.90 mmol) and EtMgBr (3.0 M in Et_2O, 0.15 mL), and stirred at −10 °C for 4 h. The reaction mixture was quenched with the addition of saturated aqueous NH_4Cl (0.3 mL) and extracted with EtOAc (2 × 20 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (SiO_2, 7% EtOAc−hexane) afforded **14** (20.8 mg, 79%) as a white solid: mp 117−118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (s, 1H), 8.11 (d, 1H, J = 8.4 Hz), 7.86 (s, 1H), 7.85 (d, 1H, J = 7.8 Hz), 7.69 (td, 1H, J = 1.1, 8.2 Hz), 7.54 (t, 1H, J = 7.3 Hz), 5.07 (s, 2H), 4.02 (s, 3H), 3.48 (s, 3H), 2.96 (q, 2H, J = 7.2 Hz), 2.27 (s, 3H), 1.22 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.6, 161.8, 154.3, 153.1, 149.1, 146.5, 134.6, 131.2, 129.3, 129.2, 127.8, 127.5, 126.9, 117.9, 114.5, 72.4, 58.7, 54.2, 35.9, 12.5, 7.8; IR (film) ν_{max} 2942, 1697, 1597, 1562, 1453, 1358, 1220, 1105, 750 cm^{-1}; FABHRMS (NBA-NaI) *m*/*e* 351.1719 (M + H$^+$, $C_{21}H_{22}N_2O_3$ requires 351.1709).

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.30; H, 5.96; N, 7.59.

Nothapodytine B (1). A solution of **14** (8.8 mg, 0.03 mmol) and 2 mL of CF_3CH_2OH saturated with HBr(g) in a sealed vessel was warmed in an 80 °C oil bath for 24 h. The brown reaction solution was treated with K_2CO_3 (40 mg) and stirred 1 h at 25 °C. The reaction mixture was filtered through SiO_2, and the filtrate was concentrated under reduced pressure. Chromatography (SiO_2, 2% MeOH−CH_2Cl_2) afforded **1** (6.7 mg, 88%) as a pale yellow solid identical with authentic material: mp 230−231 °C, lit. mp 210−215 °C ($CHCl_3$),[1] 237−238 °C (MeOH);[6b] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (s, 1H), 8.17 (d, 1H, J = 8.6 Hz), 7.90 (d, 1H, J = 8.2 Hz), 7.79 (ddd, 1H, J = 1.4, 6.9, 8.4 Hz), 7.62 (ddd, 1H, J = 1.2, 6.9, 8.1 Hz), 7.23 (s, 1H), 5.27 (s, 2H), 2.89 (q, 2H, J = 7.2 Hz), 2.27 (s, 3H), 1.22 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.5, 161.7, 152.7, 148.4, 148.1, 143.3, 131.3, 130.6, 129.3, 128.6, 128.2, 128.0, 127.8, 127.3, 98.2, 50.2, 36.0, 13.7, 7.8; IR (film) ν_{max} 1705, 1651, 1600, 1445, 1413, 1377, 1226, 1181, 1141, 761 cm^{-1}; FABHRMS (NBA-NaI) *m*/*e* 305.1299 (M + H$^+$, $C_{19}H_{16}N_2O_2$ requires 305.1290).

(±)-Mappicine ((±)-3). A solution of **1** (2.5 mg, 0.008 mmol) in 2 mL of 50% MeOH−CH_2Cl_2 under N_2 was treated with $NaBH_4$ (1.6 mg, 0.04 mmol) and stirred at 25 °C for 1 h. The reaction mixture was quenched with the addition of 0.02 mL of H_2O and concentrated under reduced pressure. The residue was dissolved in 50% EtOAc−CH_2Cl_2 and filtered through SiO_2. After removal of solvent under reduced pressure, chromatography (SiO_2, 2% MeOH−CH_2Cl_2) afforded (±)-**3** (2.0 mg, 80%) as a yellow solid.

Resolution of (±)-3. A solution of (±)-**3** in *i*-PrOH was subjected to chromatography on an analytical HPLC CHIRACEL OD column (250 mm × 4.6 mm, 10% *i*-PrOH−hexane, 1 mL/min flow rate). The effluent was monitored at 254 nm, and the enantiomers eluted with retention time of 31.4 min ((−)-**3**) and 37.5 min (*ent*-(+)-**3**), respectively (α = 1.19).

(*S*)-(−)-Mappacine ((−)-3). A solution of **1** (1.5 mg, 0.005 mmol) in anhydrous THF (3 mL) under N_2 was treated dropwise with (*S*)-BINAL-H (0.37 M in THF, 0.07 mL)[21] at −95 °C and stirred at −95 °C for 1 h. The reaction mixture was quickly warmed to −78 °C and

stirred at −78 °C for 16 h. The reaction was quenched with the addition of MeOH (0.2 mL), and the reaction mixture was filtered through SiO_2 (2% MeOH−CH_2Cl_2). The filtrate was concentrated under reduced pressure, and chromatography (SiO_2, 2% MeOH−CH_2Cl_2) afforded (−)-**3** (1.1 mg, 73%, 99.9% ee) as a yellow solid identical with authentic material: $[\alpha]^{25}_D$ −11.0 (*c* 0.0005, $CHCl_3$−MeOH 4:1) (lit.[6d] $[\alpha]^{25}_D$ −7.4° (*c* 0.1, $CHCl_3$−MeOH 4:1, 60% ee)); CD $[\theta]_{375}$ −1583° (*c* 0.0022, dioxane) (lit[2] $[\theta]_{375}$ −1524° (*c* 0.024, dioxane)); ^{1}H NMR ($CDCl_3$−CD_3OD 5:1, 400 MHz) δ 8.27 (s, 1H), 8.02 (d, 1H, J = 8.6 Hz), 7.79 (d, 1H, J = 8.2 Hz), 7.69 (ddd, 1H, J = 1.4, 6.9, 8.4 Hz), 7.51 (m, 2H), 5.152 (d, 1H, J = 1 Hz), 5.145 (d, 1H, J = 1 Hz), 4.78 (dd, 1H, J = 5.6, 7.4 Hz), 2.14 (s, 3H), 1.67 (m, 2H), 0.92 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$−CD_3OD 5:1, 100 MHz) δ 161.7, 154.8, 148.1, 131.4, 130.5, 128.52, 128.45, 128.1, 127.8, 127.5, 125.0, 100.3, 71.0, 50.0, 30.0, 11.7, 9.8; FABHRMS (NBA-NaI) *m*/*e* 307.1438 (M + H^+, $C_{19}H_{18}N_2O_2$ requires 307.1447).

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Supporting Information Available: A detailed experimental procedure and full characterization for **6** is provided (1 page). See any current masthead page for ordering and Internet access instructions.

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