The asymmetric synthesis of aryltetralin lignans: (–)-isolariciresinol dimethyl ether and (–)-deoxysikkimotoxin

Don M. Coltart and James L. Charlton

Abstract: The total asymmetric syntheses of (−)-isolariciresinol dimethyl ether (**6**) and (−)-deoxysikkimotoxin (**7**) have been carried out, in an attempt to exploit a synthetic strategy recently developed for the synthesis of (−)-deoxypodophyllotoxin (**1**, R^1 = -CH_2-, Ar = 3,4,5-trimethoxyphenyl). In so doing, a generalized method for the synthesis of aryltetralin lignans has been developed that should be applicable to a variety of substitution patterns and stereochemistries. A one-pot, 100% regio-selective reduction–lactonization procedure has been developed for the conversion of the ester **18***b* to (−)-deoxysikkimotoxin, which gave 93% isolated yield in that step.

Key words: *ortho*-quinodimethanes, lignans, Diels–Alder, asymmetric, mandelate.

Résumé : Dans le but d'exploiter une stratégie de synthèse développée récemment pour la synthèse de la (−)-désoxypodophyllotoxine (**1**, R^1 = -CH_2-, Ar = 3,4,5-triméthoxyphényle), on a réalisé la synthèse totale asymétrique de l'éther diméthylique (**6**) de (−)-isolaricirésinol et de la (−)-désoxysikkimotoxine (**7**). On a ainsi développé une méthode généralisée de synthèse des lignanes aryltétralines que l'on devrait pouvoir appliquer à une variété de stéréochimies et de patrons de substitutions. On a développé une méthode unipot, 100% régiosélective, de réduction–lactonisation qui permet d'effectuer la conversion de l'ester **18***b* en (−)-désoxysikkimotoxine; pour cette étape, le rendement en produit isolé est de 93%.

Mots clés : *ortho*-quinodiméthanes, lignanes, Diels–Alder, asymétrique, mandélate.

[Traduit par la rédaction]

Introduction

The aryltetralin lignans make up a particular subclass of natural products collectively referred to as lignans. The occurrence of lignans in nature is widespread and they have been shown to possess considerable diversity in their biological activity (1). As such, there is a substantial interest in these compounds and their synthesis.

In a recent asymmetric synthesis of the aryltetralin lignan (−)-deoxypodophyllotoxin (**1**, R^1 = -CH_2-, Ar = 3,4,5-trimethoxyphenyl), a synthetic strategy was developed, shown retrosynthetically in Scheme 1, which gave the desired compound optically pure, in 6% isolated yield (2). As a key reaction, the synthesis relied on an asymmetric [4 + 2] cycloaddition occurring between the fumarate of methyl (*S*)-mandelate (**3**), and an appropriately substituted *ortho*-quinodimethane (**4**), to give the *endo* cycloadduct **2** (Scheme 1).

The *ortho*-quinodimethane in question was obtained via thermolysis of its corresponding α-hydroxy-α-aryl-benzocyclobutenol **5**. The synthetic route to the benzocyclobutenol, and the synthetic route by which the cycloadduct was elaborated to the target molecule, were sufficiently general that it was considered possible that variation of functional groups and stereochemistry of the resulting aryltetralin lignan might be achieved without adversely affecting the synthetic strategy. Hence, to broaden the scope of the synthetic strategy in question, and consequently develop a generalized method for the synthesis of aryltetralin lignans, an attempt was made to apply the method to the total asymmetric syntheses of (−)-isolariciresinol dimethyl ether (**6**) and (−)-deoxysikkimotoxin (**7**) (Scheme 2).

An asymmetric synthesis of deoxysikkimotoxin, the 6,7-dimethoxy analogue of deoxypodophyllotoxin, has not previously been reported in the literature. To date, only two total syntheses of optically pure isolariciresinol dimethyl ether have appeared in the literature (3, 4).

Results and discussion

Benzocyclobutenol **15***a* required for the synthesis of (−)-isolariciresinol dimethyl ether was obtained as outlined in Schemes 3 and 4, following, in part, earlier work carried out by Aidhen and Narasimhan (5). The monobromination of 3,4-dimethoxybenzaldehyde (**8***a*) was carried out using bromine and acetic acid, according to a modified literature procedure (6). Recrystallization of the crude product gave pure 2-bromo-4,5-dimethoxybenzaldehyde (**9**) in 86% yield. Aldehyde **9** was protected as its ethylene glycol acetal, and then subjected to halogen exchange by exposing it to *n*-butyllithium followed by iodine. Hydrolysis of the acetal protecting group gave, in 94% yield, 2-iodo-4,5-dimethoxybenzaldehyde (**10**) (7, 8). Conversion of **10** to benzyl alcohol **11** was carried out in 96%

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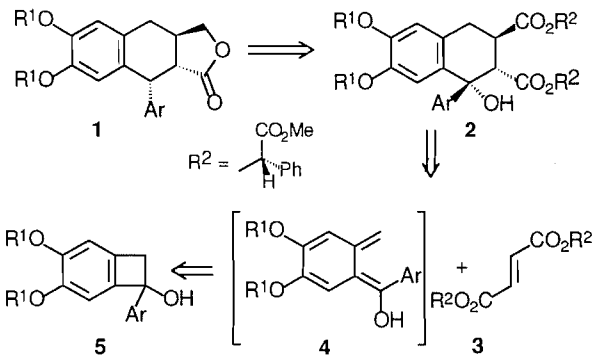
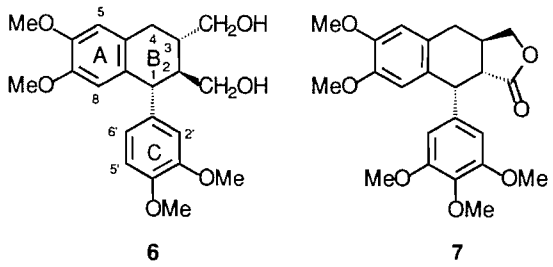
Scheme 1.



Scheme 2.

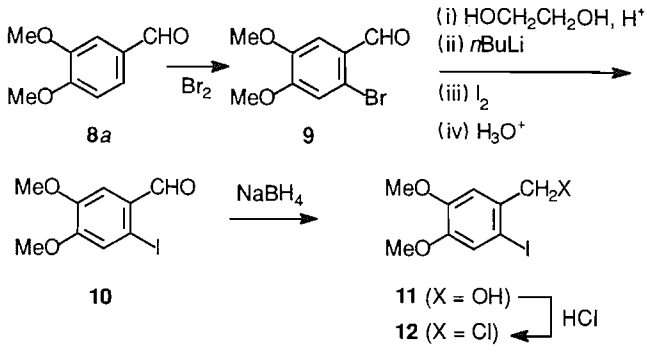


yield via sodium borohydride reduction. Exposure of **11** to hydrochloric acid afforded 2-iodo-4,5-dimethoxybenzyl chloride (**12**) in 76% overall yield from 3,4-dimethoxybenzaldehyde.

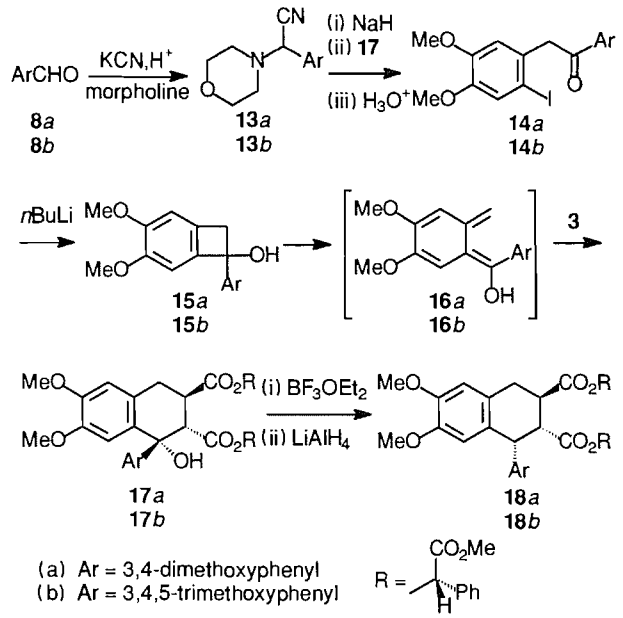
α-Aminonitrile **13***a* (Scheme 4), required for condensation with benzyl chloride **12**, was obtained using a modified Strecker synthesis (9). The reaction was originally carried out in methanol, but under these conditions it was found to give a mixture of the desired α-aminonitrile and a compound whose proton NMR spectrum corresponded to that of 3,4-dimethoxybenzaldehyde dimethyl acetal. The ratio of α-aminonitrile to acetal was 1.0 to 2.4. When carried out in ethanol, the analogous reaction gave a mixture of compound **13***a* and a compound that, based on its proton NMR spectrum, was assumed to be 3,4-dimethoxybenzaldehyde diethyl acetal, in a 2.0 to 1.1 ratio. The same reaction, using 2-propanol as the solvent, gave almost exclusive formation of the desired α-aminonitrile, with a very slight trace (less than 2%) of 3,4-dimethoxybenzaldehyde present. Presumably, the absence of acetal formation in the latter case was due to the use of a sterically hindered alcohol, a situation known to be unfavorable for acetal formation (10).

The coupling of benzyl chloride **12** and α-aminonitrile **13***a* was initiated by treating **13***a* with sodium hydride in *N*,*N*-dimethyl formamide, in order to generate its resonance-stabilized carbanion, followed by the addition of compound **12**. After acid-catalyzed hydrolysis, aryliodoketone **14***a* was obtained in 94% yield. Compound **14***a* was cyclized following the procedure of Aidhen and Narasimhan (5) by treating it with *n*-butyllithium, giving the desired benzocyclobutenol **15***a* in 74% isolated yield. It appears that metal halogen exchange with *n*-butyllithium is much faster than H abstraction or addition of *n*-butyllithium to the carbonyl group as has been noted

Scheme 3.



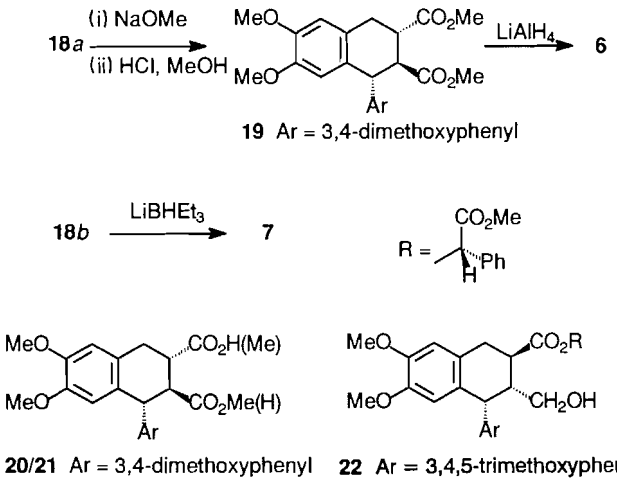
Scheme 4.



previously (refs. 5, 11, and references cited). The bromo compound analogous to **14***a* (I = Br) did not give the benzocyclobutenol **15***a* when treated with *n*-butyllithium, but gave instead material apparently derived from addition of *n*-butyllithium to the carbonyl group. This observation also parallels that of Aiden and Narasimhan (5).

Following a procedure used previously (12, 13), *ortho*-quinodimethane **16***a* was generated in refluxing toluene and trapped in situ with the fumarate of methyl (*S*)-mandelate, resulting in a 51% isolated yield of cycloadduct **17***a* after chromatography (Scheme 4). Justification for the geometry of the *ortho*-quinodimethane and the stereochemistry of the major cycloadduct has been given in an earlier publications (2, 13). Reductive removal of the C1 hydroxyl substituent from compound **17***a* was achieved according to the method of Bogucki and Charlton (2), and resulted in the formation of ester **18***a*. This gave the absolute stereochemistry at C1 required for (−)-isolariciresinol dimethyl ether. To establish the correct stereochemistry at C2 and C3, however, it was necessary to epimerize both centers. Concurrent epimerization and transesterification using sodium methoxide, followed by

Scheme 5.



work-up with dilute acid, gave a compound presumed to be either the half ester **20** or **21** (Scheme 5), which, when treated with 3% hydrochloric acid in methanol, gave the all-*trans* dimethyl ester **19** in 83% isolated yield from **18***a*. (−)-Isolariciresinol dimethyl ether was obtained from compound **19** in 96% isolated yield by reduction with lithium aluminum hydride (3).

Given that the aromatic ring A of (−)-deoxysikkimotoxin possesses the same substitution pattern as that of (−)-isolariciresinol dimethyl ether, the benzyl chloride required for the α-aminonitrile coupling reaction of the (−)-deoxysikkimotoxin synthesis was the same as that for the synthesis of (−)-isolariciresinol dimethyl ether, namely compound **12** (Scheme 3). The aromatic ring C of (−)-deoxysikkimotoxin, however, bears methoxy substituents at the 3′, 4′, and 5′ positions and, as such, the α-aminonitrile **13***b* (Scheme 4) was required for its synthesis. Compound **13***b* was obtained according to a procedure previously reported (2). The coupling of benzyl chloride **12** and α-aminonitrile **13***b* was carried out in a manner analogous to that used for the coupling of compounds **12** and **13***a*. The product of this particular reaction, aryliodoketone **14***b*, was obtained in 91% isolated yield, and was readily cyclized to benzocyclobutenol **15***b* by treatment with *n*-butyllithium. Benzocyclobutenol **15***b* was thermolyzed to *ortho*-quinodimethane **16***b* in the presence of the fumarate of methyl (*S*)-mandelate. The proton NMR spectrum of the crude reaction product showed signals consistent with those expected for cycloadduct **17***b*, and did not indicate the presence of any other cycloadducts. The cycloadduct was obtained in 57% yield after chromatography. Reductive removal of the C1 hydroxyl substituent from this compound gave the ester **18***b* in a manner analogous to that used for the formation of compound **18***a*.

Given that compound **18***b* possessed the correct absolute stereochemistry required for (−)-deoxysikkimotoxin, **7**, the possibility of obtaining the target molecule directly, via the regioselective reduction of the ester substituent at C3 followed by lactonization, was explored. The conditions that were employed initially involved the use of three equivalents of lithium triethylborohydride at room temperature. This gave a mixture consisting of (−)-deoxysikkimotoxin and starting compound **18***b* in a ratio of approximately 1 to 1, as well as a trace amount of a compound presumed to be the γ-hydroxyester **22**. When the reaction conditions were altered such that six equivalents of lithium triethylborohydride were used, no starting material could be detected, but the reaction product was still a mixture consisting of (−)-deoxysikkimotoxin and the presumed γ-hydroxyester, in a ratio favoring (−)-deoxysikkimotoxin. In an attempt to increase the regioselectivity of the reduction reaction, the temperature of the reaction was lowered to 0°C. Proton NMR analysis of the crude product in this case indicated that all of the starting material had been consumed and showed the exclusive formation of (−)-deoxysikkimotoxin. Chromatography of the crude product afforded (−)-deoxysikkimotoxin in 93% isolated yield from compound **18***b*.

Conclusion

(−)-Isolariciresinol dimethyl ether and (−)-deoxysikkimotoxin were each synthesized in an asymmetric fashion with reasonable overall yields. The overall yield of (−)-isolariciresinol dimethyl ether was 9% from 3,4-dimethoxybenzaldehyde, and the overall yield of (−)-deoxysikkimotoxin was 11% from 3,4-dimethoxybenzaldehyde. This is the first total asymmetric synthesis of deoxysikkimotoxin that has been reported.

By achieving the aforementioned syntheses, the scope of the synthetic strategy developed by Bogucki and Charlton has been broadened to allow for different substitution patterns, functionality, and stereochemistry, thereby providing a generalized procedure for the synthesis of aryltetralin lignans. In particular, it was demonstrated that the methylenedioxy substituent of aromatic ring A can be replaced without adversely affecting the reaction sequence. It was also shown that removal of the 5′ methoxy substituent of aromatic ring C does not impede the synthetic strategy in any way. As well, it was established that the functionality and stereochemistry at carbons two and three of the aryltetralin lignan could be altered by epimerization during the final steps of the strategy.

The conversion of the reduction product **18***b* to (−)-deoxysikkimotoxin was achieved in one step with an overall yield of 93%, via a reduction–lactonization reaction that proceeded with unexpectedly high regioselectivity. This represents a substantial synthetic improvement in comparison to the synthesis of (−)-deoxypodophyllotoxin carried out by Bogucki and Charlton (2). Given the similarity of these compounds to one another, it seems reasonable to conclude that a corresponding improvement in the synthesis of (−)-deoxypodophyllotoxin could also be achieved.

Experimental

The analytical instruments employed have been described in a previous publication (14).

2-Bromo-3,4-dimethoxybenzaldehyde 9

Compound **9** was synthesized by adapting a literature procedure (6). To a round-bottom flask, equipped with a mechanical stirring apparatus, was added 3,4-dimethoxybenzaldehyde (20.09 g, 120.9 mmol) and glacial acetic acid (145 mL). The resulting suspension was stirred at room temperature and, once all of the 3,4-dimethoxybenzaldehyde

had dissolved, bromine (2 equivalents, 12.5 mL, 243 mmol) was added and stirring was continued for an additional 4 h. At that point, the mixture was diluted with ice-cold water (145 mL) and allowed to stand in a refrigerator at 5°C overnight. The mixture was then filtered and the resulting solid washed with ice-cold water (100 mL), and then refiltered. The solid was then recrystallized from 80/20 (v/v) methanol–water and dried in an oven overnight at 50°C. The process yielded a light beige crystalline compound (25.6 g, 104 mmol, 86%); mp 148–150°C; IR (CH_2Cl_2): 1682 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.92 (s, 3H), 3.96 (s, 3H), 7.05 (s, 1H), 7.40 (s, 1H), 10.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 56.1 (CH_3), 56.4 (CH_3), 110.4 (CH), 115.4 (CH), 120.3 (C), 126.5 (C), 148.8 (C), 154.4 (C), 190.6 (CO); MS *m/e* (relative %): 246 (100), 245 (58), 244 (M^+, 99), 243 (53), 231 (17), 229 (16), 94 (45); HRMS calcd. for $C_9H_9{}^{79}BrO_3$: 243.9735; found: 243.9800.

2-Iodo-3,4-dimethoxybenzaldehyde 10

To a round-bottom flask was added 6-bromo-3,4-dimethoxybenzaldehyde (20.2 g, 82.3 mmol), benzene (300 mL), ethylene glycol (9.5 mL, 170.4 mmol), and *p*-toluenesulfonic acid hydrate (0.10 g, 0.53 mmol). The flask was attached to a Dean–Stark trap and refluxed for 5 h. The benzene was then evaporated to give a light yellow viscous liquid, which was filtered through silica gel (10 cm) with 50/50 (v/v) ethyl acetate/hexanes. The filtrate was evaporated to give a colorless crystalline compound. The crystals were dissolved in THF (150 mL) in a round bottom flask that was sealed with a rubber septum, flushed with nitrogen, and placed in a Dry Ice – acetone bath. At that point, *n*-butyllithium (44 mL of a 2.03 M solution in hexanes, 89 mmol) was added and the resulting solution was stirred for 15 min. Iodine (25.0 g, 98.5 mmol), dissolved in THF (80 mL), was then added and the mixture was stirred for 15 min, removed from the Dry Ice – acetone bath, and stirred for an additional 60 min. Saturated aqueous sodium bisulphite (10 mL) was added to dissipate the dark color caused by the iodine, leaving the solution light yellow. The THF portion was removed and the aqueous portion was extracted three times with ethyl acetate. The organic portions were combined and evaporated to give an oily residue. The residue was dissolved in methanol (50 mL) and to this was added 10% $HCl_{(aq)}$ (10 mL). The resulting solution was allowed to stir for 20 h at room temperature, by which time a colourless precipitate had formed. The product was extracted into CH_2Cl_2 and then evaporated to give a light colored oil. The oil was taken up in 50/50 (v/v) ethyl acetate/hexanes and filtered through silica gel (10 cm). Evaporation of the solvent gave colorless crystals (22.48 g, 77.0 mmol, 94%); mp 134–136°C; IR (CH_2Cl_2): 1695 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.92 (s, 3H), 3.96 (s, 3H), 7.31 (s, 1H), 7.41 (s, 1H), 9.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 56.1 (CH_3), 56.5 (CH_3), 92.7 (C), 111.1 (CH), 121.8 (CH), 128.4 (C), 149.7 (C), 154.4 (C), 194.8 (CO); MS *m/e* (relative %): 292 (M^+, 100), 291 (31), 277 (5), 164 (10), 136 (10); HRMS calcd. for $C_9H_9IO_3$: 291.9596; found: 291.9629.

2-Iodo-4,5-dimethoxybenzyl alcohol 11

6-Iodo-3,4-dimethoxybenzaldehyde (1.52 g, 5.20 mmol) was dissolved in 2–propanol (40 mL). $NaBH_4$ (0.232 g, 6.14 mmol) was then added and the mixture was refluxed for 12 h. The resulting solution was made just acidic by the addition of 10% $HCl_{(aq)}$ and then evaporated to a minimum volume, after which it was taken up in dichloromethane and washed with water. The aqueous portion was saturated with NaCl and extracted three times with dichloromethane. The organic portions were combined, dried with $MgSO_4$, and evaporated to give off-white crystals (1.47 g, 5.00 mmol, 96%); mp 94–96°C; IR (CH_2Cl_2): 3605 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.77 (bs, 1H), 3.84 (s, 6H), 4.56 (s, 2H), 6.98 (s, 1H), 7.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 55.8 (CH_3), 56.1 (CH_3), 68.7 (CH_2), 85.1 (C), 111.3 (CH), 121.3 (CH), 135.1 (C), 148.6 (C), 149.2 (C); MS *m/e* (relative %): 294 (M^+, 33), 166 (28), 71 (28), 69 (100), 57 (59); HRMS calcd. for $C_9H_{11}IO_3$: 293.9753; found: 293.9757.

2-Iodo-4,5-dimethoxybenzyl chloride 12

2-Iodo-4,5-dimethoxybenzyl alcohol (0.764 g, 2.60 mmol) was dissolved in dichloromethane (20 mL) and to that mixture was added glacial acetic acid (20 mL). HCl gas was passed through the resulting solution at a rate of approximately one bubble per second for 30 min. At that point, water (40 mL) was added to the solution and the organic portion was removed via a separatory funnel. The aqueous portion was then extracted twice with dichloromethane. The organic portions were combined and then washed with 10% $NaHCO_{3(aq)}$. The organic phase was removed, dried with $MgSO_4$, and evaporated to give off-white crystals (0.793 g, 2.55 mmol, 98%); mp 83–85°C; ^1H NMR ($CDCl_3$) δ: 3.85 (s, 3H), 3.86 (s, 3H), 4.63 (s, 2H), 6.96 (s, 1H), 7.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 51.2 (CH_2), 55.8 (CH_3), 56.1 (CH_3), 87.8 (C), 112.6 (CH), 121.5 (CH), 132.0 (C), 149.3 (C), 149.4 (C); MS *m/e* (relative %): 314 (M^+, 13) 312 (M^+, 36), 278 (23), 277 (100), 151 (15), 107 (18); HRMS calcd. for $C_9H_{10}{}^{35}ClIO_2$: 311.9414; found: 311.9426.

1-(3,4-Dimethoxyphenyl)-1-*N*-morpholinoacetonitrile 13*a*

3,4-Dimethoxybenzaldehyde (9.99 g, 60.1 mmol) was dissolved in 2-propanol (100 mL), in a round-bottom flask. In a separate flask KCN (3.93 g, 60.3 mmol) was dissolved in water (5 mL) and then morpholine (5.27 mL, 5.26 g, 60.4 mmol) was added with stirring, and the resulting mixture was cooled in an ice bath. At that point, concentrated HCl (4.96 mL, ca. 5.24 g, ca. 60 mmol) was added dropwise with stirring. The resulting suspension was then added all at once to the 3,4-dimethoxybenzaldehyde solution, and the final mixture was allowed to stir at room temperature for 7 days. The suspension that formed was filtered off and the filtrate was evaporated to a minimum volume, giving a viscous oil. The oil was taken up in ethyl acetate and washed with water, and the aqueous portion was subsequently extracted with ethyl acetate. The organic portions were combined, dried with $MgSO_4$, and evaporated to give a colorless crystalline compound (13.2 g, 50.3 mmol, 84%); mp 64–66°C; IR (CH_2Cl_2): 2305 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.57 (m, 4H), 3.72 (m, 4H), 3.89 (s, 3H), 3.91 (s, 3H), 4.76 (s, 1H), 6.87 (d, 1H, J = 8.3), 7.01 (d, 1H, J = 2.0), 7.10 (dd, 1H, J = 2.0, 8.3); ^{13}C NMR ($CDCl_3$) δ: 49.9 (CH_2), 56.0_0 (CH_3), 56.0_2 (CH_3), 62.1 (CH), 66.6 (CH_2), 110.8 (CH), 110.9 (CH), 115.3 (C), 120.4 (CH), 124.8 (C), 149. 2 (C), 149.6 (C); MS *m/e* (relative %): 262 (M^+, 9), 177 (23), 176 (100), 151 (27), 111 (18), 97 (34), 83 (44), 69 (73), 57 (95); HRMS: calcd. for $C_{14}H_{18}N_2O_3$: 262.1317; found: 262.1361.

Aryliodoketone 14*a*

An NaH/oil mixture (50/50, w/w, 0.457 g, 9.53 mmol with respect to NaH) was combined with DMF (10 mL) in a round-bottom flask, which was subsequently sealed with a rubber septum and flushed with nitrogen. The α-aminonitrile **13*a*** (1.66 g, 6.33 mmol), dissolved in DMF (15 mL), was then added dropwise to the suspension over a period of 5 min. Once addition was complete, the benzyl chloride **12** (1.98 g, 6.33 mmol), dissolved in DMF (15 mL), was added dropwise to the suspension over a period of 5 min, and the resulting mixture was allowed to stir at room temperature for 1 h. At that point, 10% $HCl_{(aq)}$ (10 mL) was added to the suspension and the mixture was allowed to stir for 16 h at 65°C, causing the formation of a precipitate. The precipitate was isolated from the solution and washed with cold methanol, leaving a colorless crystalline compound (2.64 g, 5.96 mmol, 94%); mp 170–172°C; IR (CH_2Cl_2): 1682 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.81 (s, 3H), 3.86 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 4.35 (s, 2H), 6.76 (s, 1H), 6.91 (d, 1H, J = 8.4), 7.26 (s, 1H), 7.57 (d, 1H, J = 2.0), 7.72 (dd, 1H, J = 2.0, 8.4); ^{13}C NMR ($CDCl_3$) δ: 49.6 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 56.1_0 (CH_3), 56.1_5 (CH_3), 89.1 (C), 110.1 (CH), 110.6 (CH), 113.2 (CH), 121.6 (CH), 123.1 (CH), 129.8 (C), 131.0 (C), 148.5 (C), 149.0 (C), 149.4 (C), 153.4 (C), 195.4 (CO); MS *m/e* (relative %): 442 (M^+, 1), 315 (26), 165 (100); HRMS calcd. for $C_{18}H_{19}O_5$ (M − I): 315.1232; found: 315.1255.

Benzocyclobutenol 15*a*

The aryliodoketone (1.64 g, 3.71 mmol) was dissolved in THF (40 mL) under a nitrogen atmosphere, and cooled in a Dry Ice – acetone bath. *n*BuLi (2.5 M in hexanes, 3.0 mL, 7.5 mmol) was then added and the mixture was allowed to stir at low temperature for 30 min. At that point, 10% $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was allowed to stir while warming to room temperature. The THF portion was removed and the aqueous portion was extracted three times with dichloromethane. The organic portions were combined, dried with $MgSO_4$, and evaporated to give a yellow semisolid that, when chromatographed on silica gel using 60/40 (v/v) ethyl acetate/hexanes, gave a colorless crystalline compound (0.869 g, 2.75 mmol, 74%); mp 136–138°C; IR (CH_2Cl_2): 3583 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.88 (bs, 1H), 3.44 (d, 1H, J = 13.4), 3.49 (d, 1H, J = 13.4), 3.84 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.78 (d, 1H, J = 8.3), 6.79 (s, 1H), 6.81 (s, 1H), 6.90 (dd, 1H, J = 2.0, 8.3), 7.06 (d, 1H, J = 2.0); ^{13}C NMR ($CDCl_3$) δ: 49.8 (CH_2), 55.9_0 (CH_3), 55.9_1 (CH_3), 56.2_0 (CH_3), 56.2_4 (CH_3), 80.5 (C), 105.3 (CH), 107.8 (CH), 109.1 (CH), 110.7 (CH), 117.8 (CH), 133.5 (C), 136.7 (C), 140.3 (C), 148.2 (C), 148.8 (C), 150.0 (C), 151.4 (C); MS *m/e* (relative %): 316 (M^+, 35), 315 (41), 301 (19), 286 (19), 285 (100), 179 (19), 165 (64), 69 (63), 55 (79); HRMS calcd. for $C_{18}H_{20}O_5$: 316.1311; found: 316.1283. Spectral data were identical to those reported for material prepared by an alternate route (12).

Cycloadduct 17*a*

This compound was prepared with slight modifications to a previously described method for the enantiomer (13). The fumarate of methyl (*S*)-mandelate (0.453 g, 1.10 mmol) was dissolved in toluene (5 mL) and heated to 98°C in an oil bath. The benzocyclobutenol **15*a*** (0.140 g, 0.44 mmol), dissolved in dichloromethane (4 mL), was then added and the mixture was allowed to boil, open to the atmosphere, until the dichloromethane had evaporated. At that point, a condenser was attached to the reaction flask and the mixture was refluxed for 48 h. The contents of the flask were then evaporated under reduced pressure, leaving a reddish-brown oil. Chromatography of the oil on silica gel with 40/60 (v/v) ethyl acetate/hexanes gave a colorless solid (0.164 g, 0.22 mmol, 51%); $[\alpha]_D^{20}$ 127.4 (*c* 0.31 g/100 mL in $CHCl_3$); IR (CH_2Cl_2): 3443 (OH), 1751 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.17 (dd, 1H, J = 11.7, 16.5), 3.44 (dd, 1H, J = 4.6, 16.5), 3.61 (s, 3H), 3.63 (s, 3H), 3.73 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), (H2 and H3 under the methoxyl signals), 5.74 (s, 1H), 5.90 (s, 1H), 6.45 (s, 1H), 6.66 (s, 1H), 6.87 (m, 2H), 6.99 (dd, 1H, J = 2.1, 8.4), 7.12 (d, 1H, J = 2.1), 7.17–7.27 (m, 3H), 7.36–7.42 (m, 3H), 7.44–7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 32.4 (CH_2), 39.7 (CH), 52.6 (CH_3), 52.8 (CH_3), 54.9 (CH), 55.7 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 56.0 (CH_3), 74.7 (CH), 74.9 (CH), 76.1 (C), 110.1 (2 × CH), 110.7 (CH), 112.1 (CH), 118.9 (CH), 125.7 (C), 127.1 (2 × CH), 127.6 (2 × CH), 128.4 (2 × CH), 128.7 (2 × CH), 129.0 (CH), 129.2 (CH), 132.4 (C), 132.8 (C), 133.2 (C), 139.2 (C), 147.9_0 (C), 147.9_3 (C), 148.5 (C), 148.7 (C), 169.3 (CO), 169.6 (CO), 171.5 (CO), 174.2 (CO); MS *m/e* (relative %): 710 (M^+ − H_2O, 29), 351 (64), 324 (40), 165 (21), 149 (64), 121 (100); HRMS calcd. for $C_{40}H_{38}O_{12}$ (M - H_2O): 710.2363; found: 710.2347. Spectral details were consistent with those reported for the enantiomer (13).

Ester 18*a*

The cycloadduct **17*a*** (0.0869 g, 0.12 mmol) was dissolved in dichloromethane (20 mL) under nitrogen, and cooled to −20°C. BF_3OEt_2 (0.10 mL, 0.80 mmol) was then added, causing the solution to turn dark blue. The mixture was cooled to −55°C and $LiAlH_4$ (0.37 M in diethyl ether, approximately 1.0 mL, approximately 0.37 mmol) was added dropwise until all of the blue had dissipated, followed by the dropwise addition of 50/50 (v/v) methanol/water (10 mL). The resulting solution was stirred for 20 min at −55°C and was then allowed to warm to room temperature. At that point, 10% $HCl_{(aq)}$ (1 mL) was added and the organic portion was separated from the aqueous portion. The aqueous portion was extracted three times with dichloromethane and the original organic portion was washed with 10% $HCl_{(aq)}$. The organic portions were combined, dried with $MgSO_4$, and evaporated to give an amorphous solid, which was chromatographed on silica gel with 30/70 (v/v) ethyl acetate/hexanes to give a colorless solid (0.0356 g, 0.05 mmol, 42%); $[\alpha]_D^{20}$ −54.3 (*c* 0.28 g/100 mL in $CHCl_3$); IR (CH_2Cl_2): 1746 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.04 (m, 1H), 3.38 (m, 2H), 3.52 (m, 1H), 3.64 (s, 3H), 3.68 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 3.73 (s, 3H), 3.87 (s, 3H), 4.56 (d, 1H, J = 5.5, H1), 5.67 (s, 1H), 6.07 (s, 1H), 6.32 (dd, 1H, J = 1.9, 8.3), 6.39 (s, 1H), 6.43 (d, 1H, J = 8.3), 6.50 (d, 1H, J = 1.9), 6.69 (s, 1H), 6.99 (d, 2H, J = 7.3), 7.08 (t, 2H, J = 7.6), 7.16–7.36 (m, 4H), 7.44–7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 31.8 (CH_2), 37.1 (CH), 45.7 (CH), 48.2 (CH), 52.4 (CH_3), 52.5 (CH_3), 55.4 (CH_3), 55.8 (3 × CH_3), 73.9 (CH), 74.6 (CH), 110.4 (2 × CH), 112.2 (CH), 112.8 (CH), 121.8 (CH), 125.6 (C), 127.0 (2 × CH), 127.9 (2 × CH), 128.2 (2 × CH), 128.6 (C), 128.7 (2 × CH), 129.2 (CH), 133.4 (C), 133.6 (C), 133.9 (C), 147.8 (C), 147.9 (C), 148.0 (C), 148.1 (C), 168.8 (CO), 169.5 (CO), 171.1 (CO), 174.2 (CO) ; MS *m/e* (relative %):

712 (M^+, 20), 563 (6), 518 (10), 485 (7), 398 (22), 397 (36), 351 (47), 325 (55), 149 (63), 121 (100); HRMS calcd. for $C_{40}H_{40}O_{12}$: 712.2520; found: 712.2502. Spectral data were consistent with those reported for the enantiomer prepared by another method (12).

Ester 19

Ester **18***a* (0.050 g, 7.02×10^{-2} mmol) was dissolved in dry methanol (10 mL) and sodium metal (0.240 g, 10.4 mmol) was added under nitrogen. The solution was stirred at reflux for 23 h. The mixture was acidified with 10% $HCl_{(aq)}$ and extracted three times with dichloromethane. The organic portions were combined, dried with $MgSO_4$, and evaporated to give a soft crystalline compound. The compound was dissolved in 3% HCl–methanol (10 mL) and stirred for 12 h. The resulting solution was extracted three times with dichloromethane and the organic portions were combined, dried with $MgSO_4$, and evaporated to give a soft crystalline compound. The compound was subsequently chromatographed on silica gel using 30/70 (v/v) ethyl acetate/hexanes to give a colourless solid (0.026 g, 5.85×10^{-2} mmol, 83%); mp 126–127°C; $[\alpha]_D^{20}$ −23.2 (*c* 0.21 g/100 mL in $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ: 31.8 (CH_2), 43.3 (CH), 48.8 (CH), 51.6_7 (CH), 51.6_9 (CH_3), 52.1 (CH_3), 55.8 (CH_3), 55.9_0 ($2 \times CH_3$), 55.9_2 (CH_3), 110.7 (CH), 110.9 (CH), 111.7 (CH), 112.1 (CH), 121.5 (CH), 126.0 (C), 129.6 (C), 135.4 (C), 147.6 (C), 147.7 (C), 148.0 (C), 148.9 (C), 174.1 (CO), 174.5 (CO). Compound **19** had ^1H NMR, IR, and mass spectral properties identical to those previously reported (3).

Isolariciresinol dimethyl ether 6

The reduction of dimethyl ester **19** was carried out using the previously described procedure (3). The dimethyl ester **19** (0.0118 g, 0.027 mmol) was dissolved in dry THF (5 mL) under nitrogen and added dropwise to a suspension of $LiAlH_4$ (0.0012 g, 0.032 mmol) in THF (5 mL) under nitrogen. The mixture was allowed to reflux for 2 h. At that point, water (2 drops) and 10% $HCl_{(aq)}$ (0.5 mL) were added and then the mixture was dried with $MgSO_4$ and evaporated to give a solid. The solid was recrystallized from ethyl acetate – hexanes to give colorless crystals (0.0102 g, 0.026 mmol, 96%); mp 150–152°C; $[\alpha]_D^{20}$ −15.3 (*c* 0.49 g/100 mL in $CHCl_3$); ^{13}C NMR ($CDCl_3$), δ: 33.2 (CH_2), 39.9 (CH), 48.0 (CH), 48.2 (CH), 53.4 (CH_3), 55.8 ($2 \times CH_3$), 56.0 (CH_3), 62.8 (CH_2), 66.5 (CH_2), 110.8 (CH), 111.1 (CH), 112.0 (CH), 113.0 (CH), 121.9 (CH), 128.2 (C), 131.8 (C), 137.7 (C), 147.1 ($2 \times C$), 147.6 (C), 149.1 (C). Compound **6** had ^1H NMR, IR, and mass spectral properties identical to those previously reported (3).

Aryliodoketone 14*b*

An NaH/oil mixture (50/50, w/w, 0.367 g, 7.65 mmol with respect to NaH) was combined with DMF (10 mL) in a round-bottom flask, which was subsequently sealed with a rubber septum and flushed with nitrogen. The α-aminonitrile **13*b*** (1.04 g, 3.57 mmol), dissolved in DMF (15 mL), was then added dropwise to the suspension over a period of 5 min. Once addition was complete, the benzyl chloride **12** (1.13 g, 3.61 mmol), dissolved in DMF (15 mL), was added dropwise to the suspension over a period of 5 min, and the resulting mixture was allowed to stir at room temperature for 1 h. At that point, 10% $HCl_{(aq)}$ (10 mL) and water (10 mL) were added to the suspension and the mixture was allowed to stir for 16 h at 65°C, causing the formation of a precipitate. The precipitate was isolated from the solution and washed with cold methanol, leaving a colorless crystalline compound (1.53 g, 3.25 mmol, 91%); mp 147–150°C; IR (CH_2Cl_2): 1684 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.81 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 3.93 (s, 6H), 4.35 (s, 2H), 6.76 (s, 1H), 7.26 (s, 1H), 7.29 (s, 2H); ^{13}C NMR ($CDCl_3$) δ: 49.8 (CH_2), 55.8 (CH_3), 56.1 (CH_3), 56.3 (CH_3), 60.8 (CH_3), 89.0 (C), 106.0 (CH), 112.8 (CH), 121.5 (CH), 130.7 (C), 131.5 (C), 142.6 (C), 148.5 (C), 149.4 (C), 152.9 (C), 195.6 (CO); MS *m/e* (relative %): 472 (M^+, 1), 344 (73), 329 (64), 195 (100); HRMS calcd. for $C_{19}H_{21}IO_6$: 472.0383; found: 472.0366.

Benzocyclobutenol 15*b*

The aryliodoketone **14*b*** (2.01 g, 4.25 mmol) was dissolved in THF (40 mL) under nitrogen, and cooled in a Dry Ice – acetone bath. *n*BuLi (2.5 M in hexanes, 3.6 mL, 9.00 mmol) was then added and the mixture was allowed to stir at low temperature for 30 min. At that point, 10% $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was allowed to stir while warming to room temperature. The THF portion was removed and the aqueous portion was extracted three times with dichloromethane. The organic portions were combined, dried with $MgSO_4$, and evaporated to give a yellow semisolid that, when chromatographed on silica gel using 50/50 (v/v) ethyl acetate/hexanes, gave a colorless crystalline compound (1.06 g, 3.05 mmol, 72%); mp 121–123°C; IR (CH_2Cl_2): 3588 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.66 (s, 1H), 3.45 (d, 1H, J = 13.4), 3.52 (d, 1H, J = 13.4), 3.81 (s, 6H), 3.83 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 6.67 (s, 2H), 6.81 (s, 1H), 6.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 50.0 (CH_2), 56.1 (CH_3), 56.2 (CH_3), 56.3 (CH_3), 60.8 (CH_3), 80.8 (C), 102.8 (CH), 105.1 (CH), 107.8 (CH), 133.7 (C), 137.2 (C), 139.6 (C), 140.0 (C), 150.1 (C), 151.6 (C), 153.0 (C); MS *m/e* (relative %): 346 (M^+, 5), 315 (7), 195 (3), 88 (10), 86 (64), 84 (100); HRMS calcd. for $C_{19}H_{22}O_6$: 346.1416; found: 346.1431.

Cycloadduct 17*b*

The fumarate of methyl (*S*)-mandelate (1.94 g, 4.70 mmol) was dissolved in toluene (10 mL) and heated in an oil bath to 98°C. The benzocyclobutenol **15*b*** (0.623 g, 1.80 mmol), dissolved in dichloromethane (4 mL), was then added and the mixture was allowed to boil, open to the atmosphere, until the dichloromethane had evaporated. At that point, a condenser was attached to the reaction flask and the mixture was refluxed for 48 h. The contents of the flask were then evaporated under reduced pressure leaving a reddish-brown oil. Chromatography of the oil on silica gel with 40/60 (v/v) ethyl acetate/hexanes gave a colorless, crystalline compound (0.779 g, 1.03 mmol, 57%), mp 82–85°C; $[\alpha]_D^{20}$ +136 (*c* 0.30 g/100 mL in $CHCl_3$); IR (CH_2Cl_2): 3475 (OH), 1741 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.17 (dd, 1H, J = 11.4, 16.4), 3.45 (dd, 1H, J = 4.3, 16.4), 3.59–3.92 (m, 2H), 3.63 (s, 6H), 3.73 (s, 3H), 3.79 (s, 6H), 3.87 (s, 3H), 3.90 (s, 3H), 5.75 (s, 1H), 5.90 (s, 1H), 6.46 (s, 1H), 6.66 (s, 1H), 6.73 (s, 2H), 6.95 (m, 2H), 7.20–7.28 (m, 2H), 7.36–7.40 (m, 4H), 7.44–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 32.3 (CH_2), 39.8 (CH), 52.6 (CH_3), 52.8 (CH_3), 54.8 (CH), 55.8 ($2 \times CH_3$; methoxy substituents on the 1,2,4,5 substituted aromatic ring), 56.2 ($2 \times CH_3$), 60.9 (CH_3), 74.7 (CH), 75.0 (CH), 76.3 (C), 104.1 ($2 \times CH$), 110.1 (CH), 112.1

(CH), 125.7 (C), 127.1 (CH), 127.6 (CH), 128.5 (CH), 128.7 (CH), 129.1 (CH), 129.3 (CH), 132.1 (C), 132.8 (C), 133.2 (C), 137.0 (C), 142.1 (C), 148.0 (C), 148.8 (C), 152.8 (C), 169.3 (CO), 169.5 (CO), 171.7 (CO), 174.1 (CO); MS *m/e* (relative %): 758 (M^+, 8), 740 (39), 548 (36), 381 (66), 355 (72), 107 (100); HRMS calcd. for $C_{41}H_{40}O_{13}$ (M − H_2O): 740.2469; found: 740.2457.

Ester 18*b*

The cycloadduct **17*b*** (0.0767 g, 0.10 mmol) was dissolved in dichloromethane (20 mL) under nitrogen, and cooled to −12°C. BF_3OEt_2 (0.10 mL, 0.81 mmol) was then added, causing the solution to turn dark blue. The mixture was cooled to −55°C and $LiAlH_4$ (0.37 M in diethyl ether, ca. 1.5 mL, ca. 0.56 mmol) was added dropwise until all of the blue had dissipated, followed by the addition of 50/50 (v/v) methanol/water (10 mL) dropwise. The resulting solution was stirred for 20 min at −55°C and was then allowed to warm to room temperature. At that point, 10% $HCl_{(aq)}$ (1 mL) was added and the organic portion was separated from the aqueous portion. The aqueous portion was extracted three times with dichloromethane and the original organic portion was washed with 10% $HCl_{(aq)}$. The organic portions were combined, dried with $MgSO_4$, and evaporated to give an off-white crystalline mass. Chromatography using silica gel and 30/70 (v/v) ethyl acetate/hexanes gave pure **18*b*** (0.0312 g, 0.043 mmol, 40%); $[\alpha]_D^{20}$ −43.0 (*c* 0.40 g/100 mL in $CHCl_3$); IR (CH_2Cl_2): 1744 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.05 (m, 1H), 3.39 (5-line m, 2H), 3.52 (6 line m, 2H), 3.58 (s, 3H), 3.63 (s, 6H), 3.69 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 3.87 (s, 3H), 4.57 (d, 1H, J = 5.5), 5.70 (s, 1H), 6.04 (s, 1H), 6.12 (s, 2H), 6.42 (s, 1H), 6.70 (s, 1H), 7.10–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$) δ: 31.8 (CH_2), 37.3 (CH), 46.2 (CH), 48.1 (CH), 52.5$_0$ (CH_3), 52.5$_4$ (CH_3), 55.8 (CH_3), 55.9 (CH_3), 56.2 (CH_3), 60.6 (CH_3), 74.1 (CH), 74.7 (CH), 107.2 (CH), 110.4 (CH), 112.2 (CH), 125.6 (C), 126.8, (CH), 127.9 (CH), 128.3 (C), 128.4 (CH), 128.7 (CH), 128.8 (CH), 129.2 (CH), 133.3 (C), 133.5 (C), 136.9 (C), 137.2 (C), 147.9 (C), 148.2 (C), 152.6 (C), 168.8 (CO), 169.4 (CO), 171.2 (CO), 174.1 (CO); MS *m/e* (relative %): 742 (M^+, 21), 578 (7), 548 (7), 515 (8), 427 (27), 381 (22), 355 (41), 149 (74), 121 (97), 107 (93), 91 (61), 77 (100); HRMS calcd. for $C_{41}H_{42}O_{13}$: 742.2625; found: 742.2575.

Deoxysikkimotoxin 7

Ester **18*b*** (0.0236 g, 3.17×10^{-5} mol) was dissolved in THF (5 mL), under nitrogen. Lithium triethylborohydride (191 μL of a 1 M solution in THF, 1.91×10^{-4} mol, 6 equivalents) was then added at 0°C, and the mixture was allowed to stir for 2 h. 10% $HCl_{(aq)}$ (5 mL) was added and the resulting solution was stirred overnight. The mixture was diluted with water and extracted three times with dichloromethane. The organic portions were combined, dried with $MgSO_4$, and evaporated to give a clear, amorphous solid that was chromatographed on silica gel using 40/60 (v/v) ethyl acetate/hexanes to give pure (−)-deoxysikkimotoxin (0.0122 g, 2.94×10^{-5} mol, 93%); $[\alpha]_D^{20}$ −85.8 (*c* 3.3 g/100 mL in $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ: 32.8$_0$ (CH_2), 32.8$_4$ (CH), 43.4 (CH), 47.7 (CH), 55.9 (CH_3), 56.0 (CH_3), 56.2 (CH_3), 60.8 (CH_3), 72.1 (CH_2), 77.2 (C), 108.3 (CH), 111.4 (CH), 113.3 (CH), 127.1 (C), 129.4 (C), 136.4 (C), 148.0 (C), 148.2 (C), 152.5 (C), 175.0 (CO); MS *m/e* (relative %): 414 (M^+, 100), 246 (13), 181 (30); HRMS calcd. for $C_{23}H_{26}O_7$: 414.1679; found: 414.1649. Compound **7** had ^1H NMR and IR spectral properties identical to those previously reported (15).

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References

1. R.S. Ward. Chem. Soc. Rev. **11**, 75 (1982), and references cited.
2. D.E. Bogucki and J.L. Charlton. J. Org. Chem. **60**, 588 (1995).
3. J.L. Charlton and M.M. Alauddin. J. Org. Chem. **51**, 3490 (1986).
4. E. Brown and A. Daugan. Tetrahedron, **45**, 141 (1989).
5. I.S. Aidhen and N.S. Narasimhan. Tetrahedron Lett. **32**, 2171 (1991).
6. A.M.B. Orr, R. Robinson, and M.M. Williams. J. Chem. Soc. **111**, 946 (1917).
7. S. Kobayashi, M. Kihara, and Y. Yamahara. Chem. Pharm. Bull. **26**, 3113 (1978).
8. F.E. Ziegler and K.W. Fowler. J. Org. Chem. **41**, 1564 (1976).
9. A. Vogel. Textbook of practical organic chemistry. 4th ed. Longman, New York. 1978, pp. 755–756.
10. A.J. Meskens. Synthesis, 501 (1981).
11. M.P. Cooke. J. Org. Chem. **58**, 6833 (1993).
12. J.L. Charlton, S.P. Maddaford, K. Koh, S. Boulet, and M.H. Saunders. Tetrahedron: Asymmetry, **4**, 645 (1993).
13. S.P. Maddaford. Ph.D. Thesis, University of Manitoba, 1994.
14. J.L. Charlton, G.L. Plourde, K. Koh, and A.S. Secco. Can. J. Chem. **68**, 2022 (1990).
15. S. Takano, N. Sato, S. Otaki, and K. Ogasawara. Heterocycles, **25**, 69 (1987).