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THE TOTAL SYNTHESIS OF RHIZOBITOXINE

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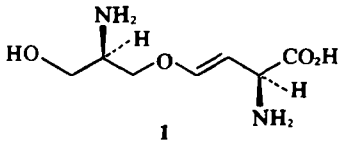
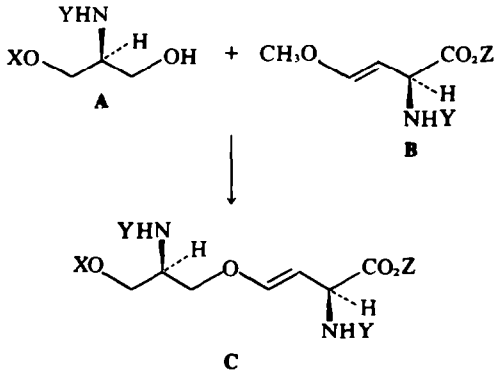
Abstract—The assignment of structure 1 to rhizobitoxine, an amino acid produced by *Rhizobium japonicum*, has been confirmed by total synthesis.

As outlined in the preceeding paper, the stereochemistry of rhizobitoxine (1) was established by the use of a novel chiroptical method.[1] We now wish to report on the total synthesis of this amino acid which confirms structure 1 in detail.



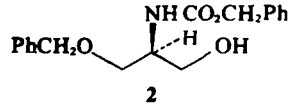
1

In our projected synthesis of rhizobitoxine, the formation of the central enol ether linkage was to be achieved by coupling fragment A, a 3-carbon alcohol, with fragment B, a 4-carbon enol ether, via a metal ion catalyzed enol ether exchange reaction to afford C (Scheme 1). Protecting groups X, Y and Z were to be selected in a manner which would permit their removal in one operation and under conditions which would leave the enol ether function and the chiral centers intact.



Scheme 1

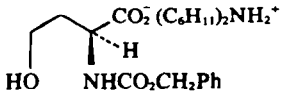
S-1-Benzyloxy-3-hydroxy-2-propylcarbamic acid benzyl ester (2) was selected as fragment A. It was synthesized in 76% yield by reduction of O-benzyl-D-serine with lithium aluminum hydride, followed by acylation of the resulting amino alcohol with benzyl chloroformate.[1]



2

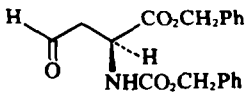
The enol ether 9 was chosen as fragment B. It was synthesized in the following manner: acylation of L-homoserine (3)[2] with benzyl chloroformate yielded the corresponding N-protected amino acid which was isolated in 54% yield as the dicyclohexylammonium salt 4. Treatment of 4 with benzyl bromide in N,N-dimethylformamide at room temperature gave a 63·5% yield of N-benzyloxycarbonyl-L-homoserine benzyl ester (5).

3: R = –H, R′ = –H
5: R = –CO_2CH_2Ph, R′ = –CH_2Ph



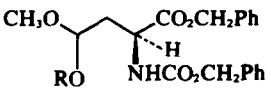
4

Oxidation of 5 with chromium trioxide/pyridine complex in methylene chloride[3] led to the aspartic semialdehyde derivative 6 (68·5%).



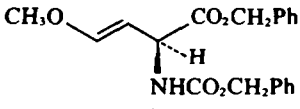
6

The corresponding dimethyl acetal 7 was formed in essentially quantitative yield upon heating the aldehyde 6 in methanol/trimethyl orthoformate solution at reflux temperature in the presence of a catalytic amount of ammonium chloride.

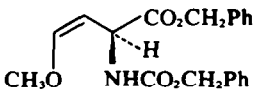


7: R = –CH_3
8: R = –$COCH_3$

Various attempts to effect elimination of methanol from acetal 7 to produce the enol ether 9 either gave starting material or caused extensive decomposition. However, treatment of acetal 7 with acetic anhydride and dry cationic exchange resin at 50° afforded the more labile hemiacetal ester 8, which upon pyrolysis under reduced pressure at 180° yielded a mixture of the *trans*-enol ether 9 and its *cis* isomer 10 (~65% from 7; ratio of *trans*/*cis*, 3:2). Since either enol ether may serve as fragment B (Scheme 1), the mixture was used for further transformation.

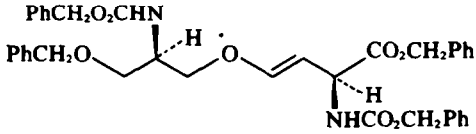


9

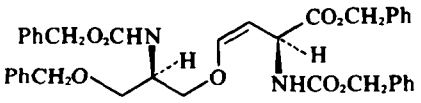


10

Dichlorobis(benzonitrile)palladium (II)[4] was found to be the agent of choice for effecting the envisaged metal ion catalyzed enol ether exchange reaction between alcohol 2 (fragment A) and the mixture of enol ethers 9 and 10 (fragment B). However, more than a catalytic amount of the reagent was required to obtain a preparatively useful amount of coupled product. Thus, treatment of a glyme solution of alcohol 2 (3 mmol) and enol ethers 9 and 10 (1 mmol)* with dichlorobis(benzonitrile)palladium (II) (0·5 mmol) at −20°C gave rise to the *trans* and *cis* enol ethers 11 and 12 in approximately a 1 : 1 ratio. The two isomers were separated by silica gel chromatography and crystallized. The mother liquors and remaining fractions containing mainly the *cis* compound were resubjected to the above reaction conditions to afford a mixture with a *trans*/*cis* ratio of 3:2. In such a manner, it was possible to convert the acetal 7 to the desired crystalline *trans* enol ether 11 in an overall yield of 17%.



11



12

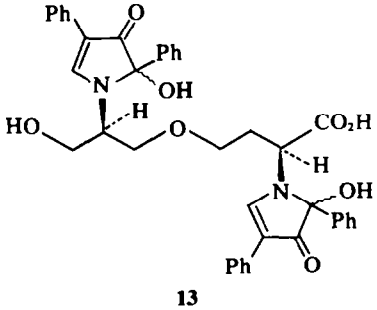
To complete the synthesis of 1, the removal of the protecting groups from enol ether 11 had to be accomplished.

A standard procedure for the cleavage of benzyl groups, such as present in 11, calls for titrating a liquid ammonia solution of the substrate with sodium until the blue color of the dissolved metal just persists.[5] However, subjection of the model compound 9 to this procedure resulted in the formation of racemic amino acid, due to the strongly basic conditions which prevail during the reduction.

In order to avoid racemization during the reduction of 11, two significant changes in the reaction conditions were made. The reaction medium was buffered with acetamide in order to suppress its basicity,[6] and an inverse mode of addition was used in the hope of reducing the time of exposure of enol ether 11 to the basic reaction conditions. Thus, addition of a glyme solution of 11 and acetamide to a solution of excess sodium in liquid ammonia at reflux temperature, followed by workup including purification by cation exchange chromatography and crystallization, gave amino acid 1 in 86% yield. The spectral and analytical properties of this material are in complete accord with the assigned structure.

The comparison of the synthetic amino acid 1 and natural rhizobitoxine proved to be a problem, since the natural material had been obtained only in the form of an amorphous solid.†[7] The NMR spectra (in D_2O) of the two materials are identical except for minor chemical shift differences, which are most probably due to a slight difference in the pH of the two sample solutions.‡ The specific rotations ($[\alpha]_D^{25}$) of the natural and synthetic materials are +51·5° and +78·8°, respectively. The low value for the natural material is a reflection of its questionable purity. We were able, however, to obtain a small amount of the crystalline hydrochloride salt of natural rhizobitoxine by crystallization from water/methanol/ether. The m.p. (175–177°) of this sample is identical to the m.p. of the synthetic hydrochloride (175–177°), while the m.m.p. is undepressed (174–178°).

Catalytic hydrogenation of synthetic 1 gave a dihydro amino acid, which upon condensation with 2 - methoxy - 2,4 - diphenyl - 3(2*H*) - furanone (MDPF)[1,8] yielded the dipyrrolinone 13.§ The CD spectrum of 13 is, within experimental error, identical to the spectrum of the corresponding material derived from natural sources.[1]



13

Thus, the molar ellipticity (θ_{390}) of the first Cotton effect in the CD-spectrum of 13 derived from synthetic 1 is +12,900 while the corresponding value for 13 derived from natural rhizobitoxine is +12,800.[1]

The synthetic amino acid 1 is therefore identical with natural rhizobitoxine, the structure of which is thus unequivocally established.

EXPERIMENTAL

M.ps are uncorrected and were determined on a Kofler Hot Stage apparatus. IR spectra were recorded on either a Perkin-

*Since McKeon *et al.* have demonstrated that equilibration of *cis* and *trans* enol ethers occurs under these reaction conditions, a mixture of 9 and 10 was used in this step.[4]

†We are indebted to Dr. L. D. Owens of the Agricultural Research Service, U.S. Department of Agriculture, Beltsville, Maryland, for a sample of natural rhizobitoxine.

‡The 220 MHz NMR spectrum of natural rhizobitoxine[7] was available for direct comparison with the 100 MHz NMR spectrum of synthetic 1.

§We thank Dr. S. De Bernardo for preparing this substance.

¶As part of our investigation of amino acids which contain an enol ether moiety, we have also prepared the enantiomer and one of the diastereomers of rhizobitoxine (1). These amino acids have been converted to derivatives analogous to 13. The CD-spectrum of the enantiomeric derivative is, within experimental error, the mirror-image of the CD-spectrum of 13, while the CD-spectrum of the diastereomeric derivative is very different from that of 13. Furthermore, the molar ellipticities (θ_{390}) of the first Cotton effects of these substances are in agreement with the predicted values.[1]

Elmer 621 or a Beckman IR-9 spectrophotometer. NMR spectra were recorded on Varian T-60 and HA-100 instruments and are reported in ppm from internal TMS. CD spectra were recorded on a Durrum-Jasco Spectro-polarimeter, Model ORD/CD/UV-5. Elemental analyses were carried out under the supervision of Dr. F. Scheidl of our Microanalytical Laboratory.

S-1-*Benzyloxy-3-hydroxy-2-propylcarbamic acid benzyl ester* (**2**)

The previously reported procedure,[1] used for the synthesis of the corresponding *R*-isomer, was also employed to make **2** (76% from O-benzyl-D-serine): m.p. 37–44°; $[\alpha]_D^{25}$ −10·89° ($CHCl_3$, *c* 0·937); NMR ($CDCl_3$) δ 7·32 (s, 5H, $PhCH_2$-), 7·29 (s, 5H, $PhCH_2$-), 5·50 (broad, 1H, NH), 5·09 (s, 2H, $PhCH_2$-), 4·48 (s, 2H, $PhCH_2$-), 3·75 (m, 5H, $-CH_2CHCH_2-$), 2·55 (broad, 1H, OH). (Found: C, 68·49; H, 6·72; N, 4·62. Calc. for $C_{18}H_{21}NO_4$: C, 68·55; H, 6·71; N, 4·44%).

Dicyclohexylammonium 2S-*benzyloxycarbonylamino-4-hydroxybutyrate* (**4**)

Benzyl chloroformate (48 g, 0·26 mol) was added dropwise to a stirred soln at room temp containing **3** (25 g, 0·24 mol), $NaHCO_3$ (51 g, 0·6 mol) and 600 ml water. After addition was completed, the soln was stirred for 2·25 hr. The resultant mixture was washed 3 times with 100 ml portions ether, acidified with conc HCl (Congo Red), and extracted 4 times with 100 ml portions ether. The ether extracts containing N-carbobenzyloxy-L-homoserine were dried over Na_2SO_4 and filtered through a cotton plug. Dicyclohexylamine was added to the filtrate until no more ppt formed. Salt **4** was collected by filtration and air-dried (56·7 g, 54%). The salt was used without further purification in the next step.

2S-*Benzyloxycarbonylamino-4-hydroxybutyric acid benzyl ester* (**5**)

The salt **4** (56·7 g, 0·13 mol) was suspended in 180 ml N,N-dimethylformamide. Benzyl bromide (16·1 ml) was added at once and the heterogeneous mixture stirred for 21 hr at room temp. The mixture was poured into 1200 ml water and the aqueous suspension extracted 5 times with 200 ml portions ether. The combined ether extracts were washed with water, satd NaCl aq, and dried over Na_2SO_4. The filtered ether soln was concentrated *in vacuo* yielding an oil which was taken up in ether/light petroleum. Two crops of crystals were collected (24 g and 6 g) and combined for recrystallization from the same solvent mixture. Pure ester **5** was collected and dried *in vacuo* (28·3 g, 63·5%): m.p. 52–57°; $[\alpha]_D^{25}$ 0° ($CHCl_3$, *c* 0·976); IR ($CHCl_3$) 3620, 3420, 1700, 1490 cm^{-1}; NMR ($CDCl_3$) δ 7·31 (s, 10H, 2 $PhCH_2$-), 5·73 (broad, 1H, NH), 5·16 (s, 2H, $PhCH_2$), 5·09 (s, 2H, $PhCH_2$-), 4·55 (m, 1H, N-CH), 3·64 (m, 2H, $HOCH_2$-), 2·78 (broad, 1H, OH), 1·95 (m, 2H, $-CH_2CH_2CH$-). (Found: C, 66·62; H, 6·12; N, 3·99. Calc. for $C_{19}H_{21}NO_5$: C, 66·46; H, 6·16; N, 4·08%).

N-*Benzyloxycarbonyl*-L-*aspartic semialdehyde benzyl ester* (**6**)

Chromium trioxide/pyridine complex[3] (62 g, 0·24 mol) was placed in a dry flask. Methylene chloride (650 ml, dried over 4A molecular sieves) was added and the mixture was stirred under argon for 5 min. Alcohol **5** (13·25 g, 38·6 mmol) in 200 ml methylene chloride (dried over 4 A molecular sieves) was then added rapidly and the mixture was stirred 15 min. The methylene chloride layer was decanted and the residue triturated several times with methylene chloride. The combined methylene chloride solns were then washed several times with small portions 1N NaOH, satd $NaHCO_3$ aq, and satd NaCl aq. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* yielding crude **6**. Material from two equal runs was combined and crystallized from ether/light petroleum yielding **6** (18 g; 68·5%): m.p. 76–78° $[\alpha]_D^{25}$ + 13·54° ($CHCl_3$, *c* 0·938); IR ($CHCl_3$) 3430, 2835, 2745, 1710, 1495 cm^{-1}; NMR ($CDCl_3$) δ 9·65 (s, 1H, $-CH_2CHO$), 7·31 (s, 10H, 2 $PhCH_2$-), 5·70 (broad, 1H, NH), 5·16 (s, 2H, $PhCH_2$-), 5·09 (s, 2H, $PhCH_2$-), 4·65 (m, 1H, N-CH), 3·05 (d, 2H, $-CH_2CHO$). (Found: C, 66·98; H, 5·52; N, 4·08. Calc. for $C_{19}H_{19}NO_5$: C, 66·85; H, 5·61; N, 4·10%).

2S-*Benzyloxycarbonylamino-4,4-dimethoxybutyric acid benzyl ester* (**7**)

Aldehyde **6** (8·8 g, 25·6 mmol) was dissolved in 135 ml methanol/trimethylorthoformate (4:1, v/v) and the resultant soln heated at reflux temp with 0·150 g ammonium chloride for 24 hr. The mixture was cooled and concentrated *in vacuo*. The residue was taken up in ether and the ether soln washed with satd $NaHCO_3$ aq and satd NaCl aq. The ether was removed *in vacuo* yielding **7** (9·9 g; 100%) as an oil: $[\alpha]_D^{25}$ −12·97° ($CHCl_3$, *c* 0·972); IR ($CHCl_3$) 3410, 1700, 1485, 1330, 1050 cm^{-1}; NMR ($CDCl_3$) δ 7·29 (s, 10H, 2 $PhCH_2$-), 5·67 (broad, 1H, NH), 5·13 (s, 2H, $PhCH_2$-), 5·09 (s, 2H, $PhCH_2$-), 4·45 (m, 1H, N-CH), 4·32 [t, 1H, $(CH_3O)_2CH$-], 3·22 and 3·20 (2S, 6H, 2 CH_3O-), 2·07 (t, 2H, $CHCH_2CH$). (Found: C, 65·03; H, 6·42; N, 3·75. Calc. for $C_{21}H_{25}NO_6$: C, 65·10; H, 6·50; N, 3·62%).

4 - *Acetoxy* - 2S - *benzyloxycarbonylamino* - 4 - *methoxybutyric acid benzyl ester* (**8**)

Acetal **7** (2·26 g, 5·82 mmol) was dissolved in 4·5 ml Ac_2O and the soln stirred at 50° with dry cation exchange resin (AG® 50W-X4; 100–200 mesh; H^+ form) for 40 min. The resin was removed by filtration and the filtrate concentrated *in vacuo* yielding **8** as an oil: NMR ($CDCl_3$) δ 3·34 (s, 3H, CH_3OCH=), 2·02 and 2·00 (2s, 3H, CH_3CO-). The crude oil was used directly in the next step.

2S - *Benzyloxycarbonylamino* - 4 - *methoxy* - trans - *but* - 3 - *enoic acid benzyl ester* (**9**) *and* 2S - *benzyloxycarbonylamino* - 4 - *methoxy* - cis - *but* - 3 - *enoic acid benzyl ester* (**10**)

The crude ester **8** was pyrolyzed by heating at 180°/0·1 mm for 1·25 hr. The pyrolyzate was taken up in a small amount ether and applied to a silica gel column (7 g) packed in ether. The column was developed with ether, and the combined fractions were treated with charcoal. The charcoal was removed by filtration through Celite and the filtrate concentrated *in vacuo* yielding a mixture of **9** and **10** as a light yellow oil (1·35 g, 65%). Analysis by high pressure liquid chromatography indicated a 3:2 ratio for **9** and **10**. The mixture was suitable for use in the next step. The *trans* and *cis* enol ethers were separated by preparative high pressure liquid chromatography (Porasil® A; $\frac{3}{8}$" × 8' column; ether/heptane, 45:55, v/v). Concentration *in vacuo* and crystallization from ether/light petroleum of the faster moving component yielded **9**: m.p. 58–60°; $[\alpha]_D^{25}$ +55° ($CHCl_3$, *c* 0·40); NMR ($CDCl_3$) δ 6·6 (d, 1H, J = 13 Hz, CH_3OCH=), 4·7 (m, 2H, CH_3OCH=$CHCH$-), 3·50 (s, 3H, CH_3OCH=). (Found: C, 67·64; H, 5·92; N, 4·07. Calc. for $C_{20}H_{21}NO_5$: C, 67·59; H, 5·95; N, 3·94%).

The fraction containing the second component was concentrated *in vacuo* yielding **10** as an oil: $[\alpha]_D^{25}$ +33·16° ($CHCl_3$, *c* 0·98); NMR ($CDCl_3$) δ 6·06 (d, 1H, J = 6 Hz, CH_3OCH=), 4·45 (dd, 1H, J = 6 and 8 Hz, CH_3OCH=$CHCH$), 3·60 (s, 3H, CH_3OCH=).

2S - *Benzyloxycarbonylamino* - 4(3 - *benzyloxy* - 2R - *benzyloxycarbonylaminopropoxy*) - trans - *but* - 3 - *enoic acid benzyl ester* (**11**) *and* 2S - *benzyloxycarbonylamino* - 4 - (3 - *benzyloxy* - 2R - *benzyloxycarbonylaminopropoxy*) - cis - *but* - 3 - *enoic acid benzyl ester* (**12**)

The previously described mixture of **9** and **10** (1·35 g, 3·81 mmol) and **2** (3·87 g, 12·3 mmol) was dissolved in dimethoxyethane (9·5 ml). NaH_2PO_4 (2·05 g, 17·1 mmol) and pulverized 4A molecular sieves (2·3 g) was added to the soln and the resultant mixture was cooled to −20°. $Pd(Cl)_2(PhCN)_2$ (0·715 g, 1·86 mmol) was added and the mixture stirred at −20° for 21 hr. The mixture was then diluted with 2 ml pyridine and 100 ml ether. The solids were removed by filtration and the filtrate concentrated *in vacuo* leaving a dark viscous oil. The oil was taken up in ether, and the soln treated with charcoal. The charcoal was removed by filtration through Celite and the filtrate concentrated yielding a light yellow oil consisting mainly of **2** and ethers **11** and **12**. Analysis by high pressure liquid chromatography indicated a 1:1 ratio for **11** and **12**. The two enol ethers were isolated by silica gel chromatography (100:1, w/w). Elution with ether/heptane (65:35; v/v) gave two

components. Crystallization of the faster moving component from ether/light petroleum gave 0·412 g (11% from 7) of **11**: m.p. 90–96°; $[\alpha]_D^{25}$+39·99° ($CHCl_3$, *c* 0·550); IR ($CHCl_3$) 3440, 1720, 1650, 1500 cm^{-1}; NMR ($CDCl_3$) δ 6·55 (d, 1H, J = 12 Hz, –OCH=CH), 4·77 (m, 2H, –OCH=CH–CH–), 3·75 (m, 2H, CH_2O), 3·55 (m, 2H, CH_2O). (Found: C, 69·50; H, 6·12; N, 4·26). Calc. for $C_{37}H_{38}N_2O_8$: C, 69·58; H, 6·00; N, 4·39%).

Crystallization of the slower moving component from ether/light petroleum gave 0·035 g of **12**: m.p. 65–75°; $[\alpha]_D^{25}$ +48·02° ($CHCl_3$, *c* 0·556); IR ($CHCl_3$) 3440, 1710, 1660, 1500 cm^{-1}; NMR ($CDCl_3$) δ 6·06 (d, 1H, J = 6 Hz, –OCH=CH–). (Found: C, 69·62; H, 6·03; N, 4·31. Calc. for $C_{37}H_{38}N_2O_8$: C, 69·58; H, 6·00; N, 4·39%).

By resubjecting the fractions and mother liquors containing mainly the *cis* enol ether **12** to the conditions of the exchange reaction, a mixture of the *trans* and *cis* enol ethers **11** and **12** (3:2) was obtained. In such a manner it was possible to realize a 17% yield of crystalline **11** from acetal **7**.

Rhizobitoxine (**1**)

Sodium metal (0·115 g, 5 mg-atom) was added to 25 ml liquid ammonia, which had been dried with and distilled from Na. A soln consisting of acetamide (0·16 g 2·7 mmol) and **11** (0·31 g; 0·485 mol) in 2·5 ml dimethoxyethane was added carefully to the ammonia soln. The mixture was then stirred at reflux temp for 25 min. The blue color of Na was discharged by the cautious addition of NH_4Cl (0·275 g, 5·1 mmol) and the ammonia allowed to evaporate. The residue was dissolved in water and the pH adjusted to 2·5 with 1N HCl (gas evolution). The aqueous soln was applied to a cation exchange column (AG® 50W-X4; 100–200 mesh; H^+ form). The column was washed with water and 10% aqueous pyridine. The amino acid **1** was eluted with 1·5N NH_4OH. The fraction was concentrated *in vacuo* yielding crystalline **1**, (80 mg, 86%): m.p. 175–179°; $[\alpha]_D^{25}$ +78·85° (H_2O, *c* 0·410); NMR (D_2O) δ 7·28 (d, 1H, J = 13 Hz, –OCH=CHCH–), 5·52 (dd, 1H, J = 10 and 13 Hz, –OCH=CHCH–), 4·60 (d, 1H, J = 10 Hz, –OCH=CHCH–), 4·35 (dd, 2H, J = 3 and 5 Hz, CH_2–O), 4·15 (dd, 2H, J = 6 and 8 Hz, CH_2–O), 3·74 (q, 1H, J = 6 Hz, –CH_2CHCH–). (Found: C, 44·03; H, 7·51; N, 14·38. Calc. for $C_7H_{14}N_2O_4$: C, 44·21; H, 7·42; N, 14·73%).

Addition of 1 equivalent of 0·1 N HCl to rhizobitoxine, followed by concentration and crystallization from water/methanol/ether gave the monohydrochloride salt: m.p. 175–177°; $[\alpha]_D^{25}$ +71·6° (H_2O, *c* 0·36). (Found: C, 36·14; H, 6·91; N, 12·23. Calc. for $C_7H_{14}N_2O_4 \cdot HCl \cdot 0.3\,H_2O$: C, 36·23; H, 6·78; N, 12·07%). A mixture m.p. of the synthetic monohydrochloride with the monohydrochloride of the natural amino acid was found to be 174–178°.

Dihydrorhizobitoxine

Synthetic rhizobitoxine was reduced as described previously[1] yielding dihydrorhizobitoxine. The crude amino acid was used directly in the next reaction.

Derivatization of synthetic dihydrorhizobitoxine

Synthetic dihydrorhizobitoxine was derivatized with MDPF as described in the previous paper[1] yielding **13** (58%): IR (KBr) 1660, 1605, 1570, 1498, 1450, 1370, 1235, 1105, 1070, 1030, 965, 910, 790, 755, 695 cm^{-1}; CD (0·001M, EtOH) $[\theta]_{446}$ 0, $[\theta]_{393}$ +12,900 (max), $[\theta]_{349}$ 0, $[\theta]_{325}$ −9600 (min), $[\theta]_{304}$ 0, $[\theta]_{290}$ +9000 (max), $[\theta]_{261}$ 0 (min), $[\theta]_{210}$ +30,000 (max).

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