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A Synthetic Approach to (+)-Dioncophylline C

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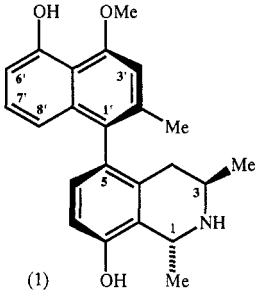
Abstract

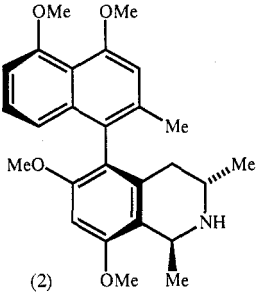
In a synthetic approach to (+)-dioncophylline C (1), a coupling between the chiral oxazoline (3) and the Grignard reagent obtained from bromide (4) gave the major biaryl (5) and the minor biaryl (12) in good yield and high diastereoselectivity (yield 70%; ratio 91:9). The stereochemistry of the major biaryl (5) was confirmed by X-ray structure analysis of the derived crystalline iodide salt (13).

(+)-Dioncophylline C (1)[1] is an example of the unusual family of naphthylisoquinoline alkaloids which have been isolated from the plant families Dioncophyllaceae and Ancistrocladaceae. Compound (1) is the only 5–1′ linked Dioncophyllaceae alkaloid isolated thus far and the absolute configuration depicted was determined by a combination of chiroptical and chemical methods.[1]

We have recently reported a formal synthesis of (−)-*O*-methylancistrocladine (2)[2] in which the biaryl linkage was constructed with high diastereoselectivity by utilizing the asymmetric biaryl coupling method developed by Meyers.[3] It



(1)



(2)

[1] Bringmann, G., Rübenacker, M., Weirich, R., and Aké Assi, L., *Phytochemistry*, 1992, **31**, 4019.
[2] Leighton, B. N., and Rizzacasa, M. A., *J. Org. Chem.*, 1995, **60**, 5702.
[3] Meyers, A. I., and Lutomski, K. A., *J. Am. Chem. Soc.*, 1982, **104**, 879; Meyers, A. I., and Himmelsbach, R. J., *J. Am. Chem. Soc.*, 1985, **107**, 682; Meyers, A. I., Flisak, J. R., and Aitken, R. A., *J. Am. Chem. Soc.*, 1987, **109**, 5446; Warshawsky, A. M., and Meyers, A. I., *J. Am. Chem. Soc.*, 1990, **112**, 8090; Meyers, A. I., Meier, A., and Rawson, D. J., *Tetrahedron Lett.*, 1992, **33**, 853.

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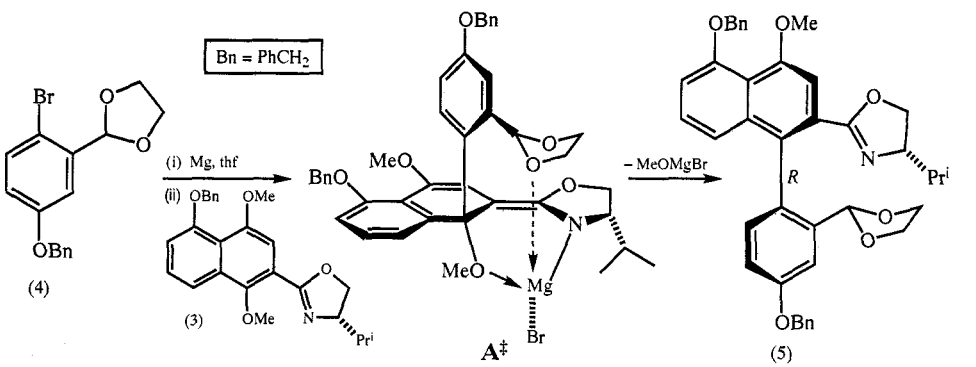
has been shown that these couplings proceed under chelation control and that the outcome can be controlled by adjusting the chelating ability of the *ortho* substituents on the Grignard reagent.[4] For a synthesis of (+)-dioncophylline C (1), a coupling between the chiral oxazoline (3) and the Grignard reagent derived from the bromide (4) would be required (Scheme 1). The reaction should proceed via the transition state[4] $\mathbf{A}^{\ddagger}$, where chelation to the dioxolan oxygen atoms by the magnesium atom would predominate,[4,5] to provide the desired biaryl (5) as the major product. The atropisomer (5) could then be converted into the natural product (1) by using previously developed procedures.[5,6]

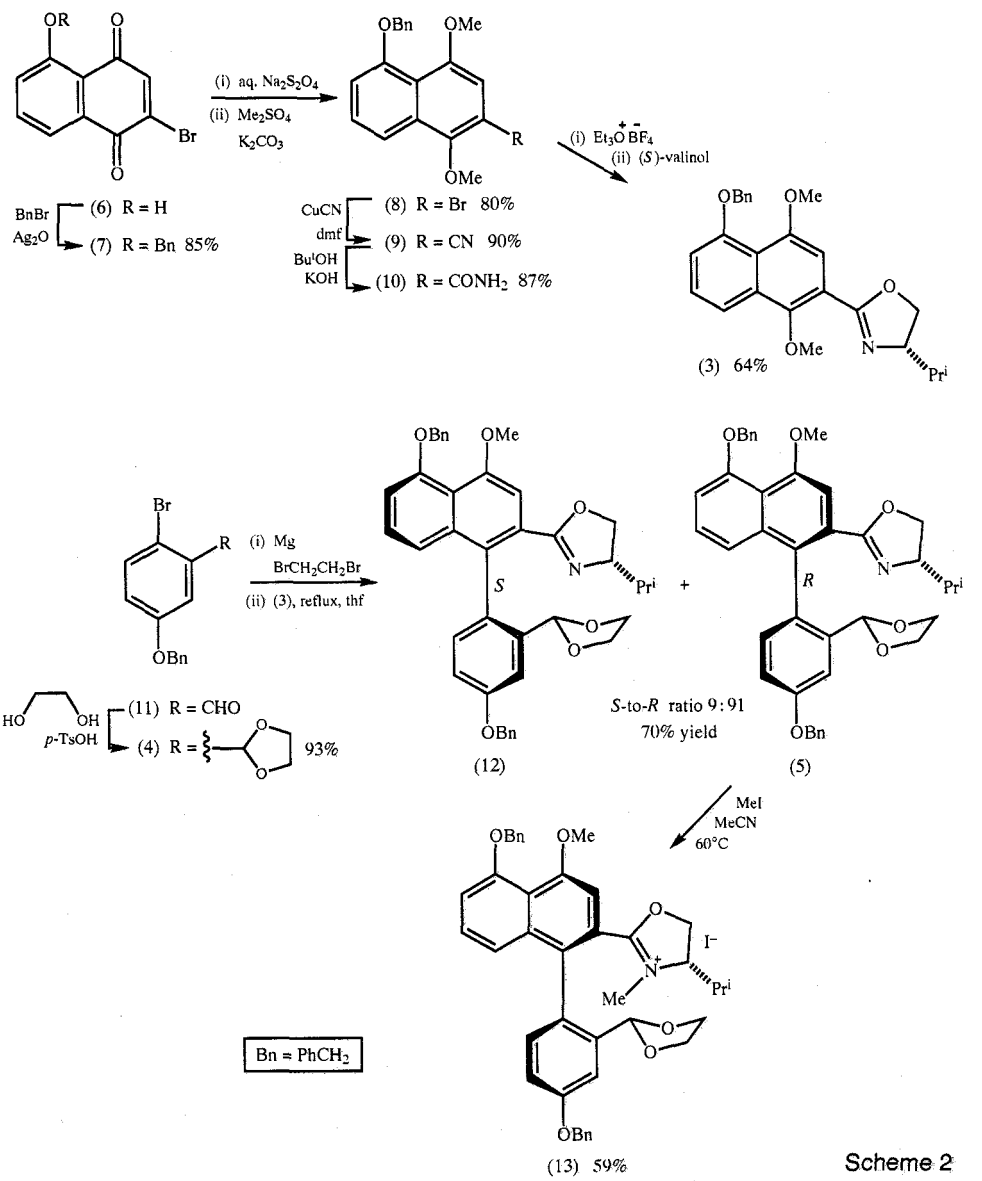


Scheme 1

We proceeded to investigate the above proposal and the results are outlined in Scheme 2. Conversion of bromo quinone (6)[7] into naphthalene (8) via the ether (7) was achieved according to the procedure described by Jung (Scheme 2).[8] Treatment of bromide (8) with cuprous cyanide in boiling dimethylformamide gave nitrile (9) and subsequent base hydrolysis then provided amide (10) which was converted into oxazoline (3) by treatment with triethyloxonium tetrafluoroborate followed by (*S*)-valinol.[2] The required bromide (4) was prepared by acetalization of known aldehyde (11);[9] generation[10] of the Grignard reagent, followed by addition of a solution of oxazoline (3) in tetrahydrofuran and heating for 16 h gave the minor (*S*)-isomer (12) (6%) and the desired major (*R*)-isomer (5) (64%), after purification by flash chromatography. The stereochemical outcome of the coupling was confirmed by an X-ray structural determination conducted on the iodide salt (13) (Fig. 1) which was obtained by treatment of the biaryl (5) with methyl iodide in acetonitrile.

[4] Meyers, A. I., and Moorlag, H., *Tetrahedron Lett.*, 1993, **34**, 6989.
[5] Rizzacasa, M. A., and Sargent, M. V., *J. Chem. Soc., Perkin Trans. 1*, 1991, 2773.
[6] Rizzacasa, M. A., and Sargent, M. V., *J. Chem. Soc., Perkin Trans. 1*, 1991, 845.
[7] Jung, M. E., and Hagenah, J. A., *J. Org. Chem.*, 1987, **52**, 1889.
[8] Jung, M. E., and Jung, Y. H., *Tetrahedron Lett.*, 1988, **29**, 2517.
[9] Keserű, G. M., Mezey-Vándor, G., Nógrádi, M., Vermes, B., and Kajtár-Peredy, M., *Tetrahedron*, 1992, **48**, 913.
[10] Lai, Y. H., *Synthesis*, 1981, 585.

Since the biaryl (5) possesses one less *ortho* substituent about the biaryl linkage, racemization could occur under the reaction conditions, and the observed ratio of products would therefore be the result of a thermodynamic equilibrium. However, when a solution of atropisomer (5) in tetrahydrofuran was boiled for 24 h, no rotation about the biaryl linkage was detected to the limits of ^{1}H n.m.r. spectroscopy. This observation supports the view that the observed selectivity is due to kinetic control. An interesting aspect of the 300-MHz ^{1}H n.m.r. spectrum of (13) was the large chemical shift difference (0·53 ppm) between the diastereotopic methyl groups on the isopropyl substituent. It appears that the conformation of the salt (13) in solution could be similar to that in the solid



Scheme 2

state as the X-ray structure (Fig. 1) shows one methyl group [C(7‴)] positioned in the shielding zone of the benzene ring.

The X-ray structure of the salt (13) provides further evidence that these couplings proceed under chelation control and that good selectivities can be achieved.

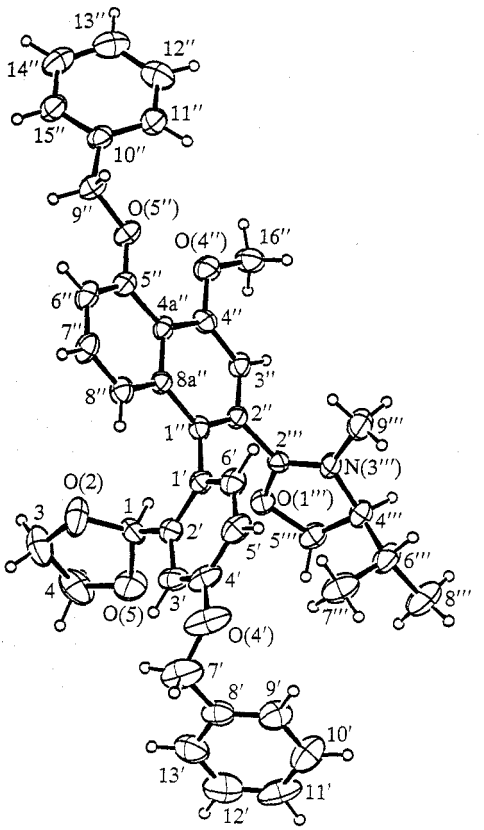


Fig. 1. ORTEP diagram of the cation (13) showing the crystallographic labelling scheme; carbon atoms are depicted by numerals only. Ellipsoids are at the 50% probability level.

Description of the Structure (Fig. 1 and Tables 1–3)

Selected bond lengths, angles and torsion angles are given in Tables 2 and 3. The 10 atoms of the naphthalene ring are planar, the maximum deviation being −0·015(6) Å for C(7″). The methoxy group and C(9″) and O(5″) of the benzyloxy group lie almost in the plane of the naphthalene moiety, with the C(3″)–C(4″)–O(4″)–C(16″) and C(6″)–C(5″)–O(5″)–C(9″) torsion angles being −1·5(9) and 3·9(9)° respectively, while the dihedral angle between the naphthalene ring and the benzyloxy aromatic ring [maximum deviation: C(12″) 0·014(7) Å] is 37·1(2)°. In contrast, the oxazoline ring [maximum deviation: O(1‴) −0·037(4) Å], attached to C(2″), and the trisubstituted benzene ring [maximum deviation: C(4′) −0·007(5) Å], attached to C(1″), both lie almost perpendicular to the naphthalene ring, with the dihedral angles being 84·3(2) and 83·40(15)°, respectively. For the second benzyloxy group, attached to C(4′), both C(7′) and

Table 1. Final fractional atomic coordinates and equivalent isotropic temperature factors for (13)

Estimated standard deviations are given in parentheses

$U_{eq} = \frac{1}{3} \Sigma\Sigma\, U_{ij}\, \mathbf{a}_i^*\, \mathbf{a}_j^*\, \mathbf{a}_i . \mathbf{a}_j$

Atom	x	y	z	U_{eq} (Å^2)
I	0·21032(8)	0·77945(3)	−0·08866(4)	0·1228(3)
C(1)	0·4376(9)	0·3980(3)	0·1802(3)	0·067(2)
O(2)	0·4859(8)	0·3305(3)	0·1812(3)	0·113(2)
C(3)	0·527(2)	0·3144(5)	0·2459(5)	0·116(4)
C(4)	0·4808(14)	0·3727(6)	0·2877(4)	0·122(4)
O(5)	0·3937(8)	0·4115(3)	0·2449(2)	0·107(2)
C(1′)	0·3575(7)	0·4288(3)	0·0661(3)	0·051(2)
C(2′)	0·3279(7)	0·4074(3)	0·1304(3)	0·057(2)
C(3′)	0·1954(9)	0·3902(3)	0·1466(4)	0·074(2)
C(4′)	0·0961(8)	0·3934(4)	0·1002(5)	0·079(2)
O(4′)	−0·0361(6)	0·3739(4)	0·1088(4)	0·120(3)
C(5′)	0·1235(9)	0·4156(4)	0·0349(5)	0·078(2)
C(6′)	0·2534(8)	0·4322(4)	0·0202(4)	0·069(2)
C(7′)	−0·0815(14)	0·3550(6)	0·1710(7)	0·130(5)
C(8′)	−0·1173(9)	0·4154(4)	0·2157(4)	0·082(2)
C(9′)	−0·1776(10)	0·4719(6)	0·1905(4)	0·097(3)
C(10′)	−0·2167(12)	0·5255(6)	0·2325(7)	0·123(4)
C(11′)	−0·1967(13)	0·5179(8)	0·3006(6)	0·124(4)
C(12′)	−0·1363(14)	0·4618(8)	0·3234(6)	0·128(4)
C(13′)	−0·0943(12)	0·4105(6)	0·2824(5)	0·106(3)
C(1″)	0·4958(7)	0·4460(3)	0·0434(3)	0·051(2)
C(2″)	0·5496(7)	0·5112(3)	0·0493(3)	0·052(2)
C(3″)	0·6723(7)	0·5295(3)	0·0227(3)	0·057(2)
C(4″)	0·7480(7)	0·4831(3)	−0·0113(3)	0·053(2)
O(4″)	0·8680(5)	0·4994(2)	−0·0403(2)	0·0705(13)
C(4a″)	0·6996(7)	0·4130(3)	−0·0201(3)	0·0487(13)
C(5″)	0·7727(7)	0·3599(3)	−0·0560(3)	0·058(2)
O(5″)	0·8929(5)	0·3781(2)	−0·0821(2)	0·0679(12)
C(6″)	0·7164(8)	0·2950(3)	−0·0618(3)	0·069(2)
C(7″)	0·5931(8)	0·2799(3)	−0·0346(4)	0·074(2)
C(8″)	0·5232(8)	0·3271(3)	−0·0001(3)	0·063(2)
C(8a″)	0·5741(7)	0·3957(3)	0·0084(3)	0·0516(14)
C(9″)	0·9635(8)	0·3291(4)	−0·1216(4)	0·076(2)
C(10″)	1·0969(8)	0·3596(4)	−0·1401(3)	0·067(2)
C(11″)	1·1107(10)	0·4275(4)	−0·1611(4)	0·085(2)
C(12″)	1·2358(12)	0·4523(6)	−0·1776(5)	0·101(3)
C(13″)	1·3453(12)	0·4108(7)	−0·1759(5)	0·105(3)
C(14″)	1·3320(10)	0·3435(6)	−0·1554(5)	0·099(3)
C(15″)	1·2085(10)	0·3183(5)	−0·1369(4)	0·087(2)
C(16″)	0·9126(9)	0·5695(4)	−0·0353(5)	0·083(2)
O(1‴)	0·4765(5)	0·5710(2)	0·1480(2)	0·0639(12)
C(2‴)	0·4697(7)	0·5656(3)	0·0826(3)	0·0513(14)
N(3‴)	0·3974(7)	0·6108(3)	0·0548(3)	0·071(2)
C(4‴)	0·3408(8)	0·6608(3)	0·1034(4)	0·076(2)
C(5‴)	0·4056(9)	0·6344(3)	0·1675(4)	0·073(2)
C(6‴)	0·1875(9)	0·6651(4)	0·1036(4)	0·089(3)
C(7‴)	0·1226(11)	0·5966(5)	0·1230(6)	0·110(3)
C(8‴)	0·1477(13)	0·7255(6)	0·1477(6)	0·122(4)
C(9‴)	0·381(2)	0·6193(6)	−0·0174(4)	0·134(5)
O(w)	0·176(3)	0·2327(13)	0·2455(12)	0·223(10)

O(4′) again lie almost in the ring plane, with the C(3′)–C(4′)–O(4′)–C(7′) torsion angle being 6·8(12)°, and the dihedral angle between the benzyloxy aromatic ring [maximum deviation: C(13′) 0·014(8) Å] and trisubstituted benzene ring being 76·5(3)°. The dioxolan ring adopts a regular half-chair conformation,[11] with the maximum deviation from the least-squares plane being O(5) −0·174(7) Å; torsion angles for this ring are given in Table 3.

Table 2. Selected bond lengths (Å) and angles (degrees) for (13)

Atoms	Bond length	Atoms	Angle
C(1)–O(2)	1·389(8)	O(2)–C(1)–O(5)	105·7(6)
C(1)–O(5)	1·394(8)	O(2)–C(1)–C(2′)	112·2(6)
C(1)–C(2′)	1·489(10)	O(5)–C(1)–C(2′)	111·8(7)
O(2)–C(3)	1·397(10)	C(1)–O(2)–C(3)	108·9(6)
C(3)–C(4)	1·478(14)	O(2)–C(3)–C(4)	105·4(8)
C(4)–O(5)	1·431(12)	O(5)–C(4)–C(3)	104·4(7)
C(2″)–C(2‴)	1·476(8)	C(1)–O(5)–C(4)	105·7(7)
O(1‴)–C(2‴)	1·318(7)	C(2‴)–O(1‴)–C(5‴)	107·9(5)
O(1‴)–C(5‴)	1·466(8)	N(3‴)–C(2‴)–O(1‴)	114·4(5)
C(2‴)–N(3‴)	1·261(8)	N(3‴)–C(2‴)–C(2″)	126·9(5)
N(3‴)–C(9‴)	1·465(10)	O(1‴)–C(2‴)–C(2″)	118·6(5)
N(3‴)–C(4‴)	1·482(8)	C(2‴)–N(3‴)–C(9‴)	125·2(6)
C(4‴)–C(5‴)	1·525(10)	C(2‴)–N(3‴)–C(4‴)	112·1(5)
C(4‴)–C(6‴)	1·527(12)	C(9‴)–N(3‴)–C(4‴)	122·3(6)
		N(3‴)–C(4‴)–C(5‴)	100·2(5)
		N(3‴)–C(4‴)–C(6‴)	114·6(7)
		C(5‴)–C(4‴)–C(6‴)	115·9(7)
		O(1‴)–C(5‴)–C(4‴)	104·9(5)

Table 3. Selected torsion angles (degrees) for (13)

Atoms	Angle	Atoms	Angle
O(5)–C(1)–O(2)–C(3)	−25·9(11)	O(1‴)–C(2‴)–N(3‴)–C(4‴)	1·8(9)
C(2′)–C(1)–O(2)–C(3)	−148·0(9)	C(2″)–C(2‴)–N(3‴)–C(4‴)	−175·1(6)
C(1)–O(2)–C(3)–C(4)	8·9(13)	C(2‴)–N(3‴)–C(4‴)–C(5‴)	2·6(8)
O(2)–C(3)–C(4)–O(5)	10·7(14)	C(9‴)–N(3‴)–C(4‴)–C(5‴)	−171·1(10)
O(2)–C(1)–O(5)–C(4)	32·4(10)	C(2‴)–N(3‴)–C(4‴)–C(6‴)	−122·2(8)
C(2′)–C(2)–O(5)–C(4)	154·7(7)	C(9‴)–N(3‴)–C(4‴)–C(6‴)	64·1(12)
C(3)–C(4)–O(5)–C(1)	−26·4(12)	C(2‴)–O(1‴)–C(5‴)–C(4‴)	6·9(8)
O(1‴)–C(2‴)–N(3‴)–C(9‴)	175·3(10)	N(3‴)–C(4‴)–C(5‴)–O(1‴)	−5·5(7)
C(2″)–C(2‴)–N(3‴)–C(9‴)	−1·7(14)	C(6‴)–C(4‴)–C(5‴)–O(1‴)	118·4(7)

Experimental

General methods have been given previously.[12]

5-Benzyloxy-2-bromonaphthalene-1,4-dione (7)

To a solution of the naphthoquinone (6)[7] (2·0 g, 7·9 mmol) and benzyl bromide (1·61 ml, 13·5 mmol) in CH_2Cl_2 (50 ml) was added silver oxide (1·58 g, 6·8 mmol) and the resulting suspension was stirred at room temperature for 43 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to yield the crude product. Purification by flash chromatography with 10–40% EtOAc/petrol as eluent gave the quinone (7) (2·06 g, 75%) which was recrystallized from ethanol as orange needles, m.p. 123·5–124°

[11] Altona, C., Geise, H. J., and Romers, C., *Tetrahedron*, 1968, **24**, 13.
[12] Gable, R. W., McVinish, L. M., and Rizzacasa, M. A., *Aust. J. Chem.*, 1994, **47**, 1537.

(lit.[8] 125°) (Found: C, 59·7; H, 3·0; Br, 23·3. Calc. for $C_{17}H_{11}BrO_3$: C, 59·5; H, 3·2; Br, 23·3%). ^{1}H n.m.r. δ 5·30, s, $PhCH_2O$; 7·32–7·43, m, 5H, ArH; 7·54–7·57, m, 2H, ArH; 7·61, dd, J 7·8, 7·5 Hz, H7; 7·82, dd, J 7·8, 1·2 Hz, H6 or H8. ^{13}C n.m.r. δ 70·9, 120·1, 120·9, 126·6, 128·0, 128·7, 133·1, 134·8, 135·7, 136·8, 142·2, 158·8, 160·4, 178·2, 181·2.

5-Benzyloxy-2-bromo-1,4-dimethoxynaphthalene (8)

A suspension of the naphthoquinone (7) (1·81 g, 5·3 mmol) in ether (25 ml) was shaken with a solution of sodium dithionite (2·42 g, 10·4 mmol) in water (25 ml) until the bright yellow colour dissipated (approx. 20 min) to give a clear solution. The organic layer was separated and washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a tan solid. A solution of the crude diol in acetone (75 ml) was heated under reflux with potassium carbonate (5·61 g, 40·6 mmol) and dimethyl sulfate (3·4 ml, 35·3 mmol) for 24 h. The cooled suspension was then filtered and concentrated under reduced pressure, and the resulting residue was dissolved in ether and treated with triethylamine (20 ml) for 20 min at room temperature. The ether solution was washed with 1 M HCl, water, and removal of the solvent gave the crude product which was purified by chromatography on basic alumina with 5% EtOAc/petrol as eluent. Recrystallization from petrol gave the *naphthalene* (8) (1·57 g, 80%) as colourless prisms, m.p. 91–92° (lit.[8] 86–87°) (Found: C, 61·4; H, 4·5; Br, 21·5. Calc. for $C_{19}H_{17}BrO_3$: C, 61·2; H, 4·6; Br, 21·4%). ^{1}H n.m.r. δ 3·93, s, OMe; 3·94, s, OMe; 5·20, s, $PhCH_2O$; 6·92, s, H3; 6·98, dd, J 7·8, 0·9 Hz, H6 or H8; 7·32–7·47, m, 4H, ArH; 7·58–7·60, m, 2H, ArH; 7·73, dd, J 8·7, 0·9 Hz, H6 or H8. ^{13}C n.m.r. δ 56·1, 61·2, 71·4, 109·1, 109·7, 112·6, 115·1, 118·1, 126·9, 127·5, 127·6, 128·3, 131·8, 137·3, 146·6, 154·0, 156·5.

5-Benzyloxy-1,4-dimethoxynaphthalene-2-carbonitrile (9)

A mixture of the naphthalene (8) (0·5 g, 1·3 mmol) and cuprous cyanide (0·31 g, 3·4 mmol) in dimethylformamide (10 ml) was heated at reflux under nitrogen for 23 h. The reaction mixture was allowed to cool to room temperature and poured into a solution of ethane-1,2-diamine (1 ml) in water (10 ml). The aqueous suspension was extracted with EtOAc and the resulting organic layer was washed with water until the aqueous layer was colourless. Removal of the solvent gave a tan solid which was purified by filtration through a plug of silica with 10–20% EtOAc/petrol as eluent. Recrystallization from petrol gave colourless needles of the *nitrile* (9) (0·39 g, 90%), m.p. 125–125·5° (Found: C, 75·3; H, 5·2; N, 4·3. $C_{20}H_{17}NO_3$ requires C, 75·2; H, 5·4; N, 4·4%). ν_{max} (KBr disk) 2226 cm^{-1}. ^{1}H n.m.r. δ 3·93, s, OMe; 4·15, s, OMe; 5·21, s, $PhCH_2O$; 6·75, s, H3; 7·12, dd, J 7·8, 1·1 Hz, H6 or H8; 7·33–7·58, m, 6H, ArH; 7·80, dd, J 8·4, 1·2 Hz, H6 or H8. ^{13}C n.m.r. δ 56·5, 62·8, 71·5, 100·1, 105·1, 111·9, 115·7, 117·1, 126·9, 127·7, 128·0, 128·4, 130·7, 136·9, 153·5, 154·8, 156·4, 160·4.

5-Benzyloxy-1,4-dimethoxynaphthalene-2-carboxamide (10)

A solution of the nitrile (9) (1·65 g, 5·2 mmol) in Bu^{t}OH (50 ml) was heated under reflux with powdered potassium hydroxide (1·65 g, 29·4 mmol) for 3 h. The cooled solution was poured into water, then extracted with CH_2Cl_2, and the organic layer was washed with saturated NaCl and dried over $MgSO_4$. Removal of the solvent gave the crude amide which was purified by flash chromatography on silica gel with 80% EtOAc/petrol as eluent. Recrystallization from EtOAc gave the *amide* (10) (1·52 g, 87%) as colourless needles, m.p. 167–167·5° (Found: C, 71·2; H, 5·4; N, 4·1. $C_{20}H_{19}NO_4$ requires C, 71·2; H, 5·7; N, 4·2%). ^{1}H n.m.r. δ 3·94, s, OMe; 4·00, s, OMe; 5·21, s, $PhCH_2O$; 6·25, br s, 1H; 7·05, d, J 7·8 Hz, 1H, ArH; 7·33–7·60, m, 7H, ArH; 7·76, d, J 8·1 Hz, 1H, ArH; 8·00, br d, J 2·7 Hz, 1H. ^{13}C n.m.r. δ 56·1, 62·8, 71·5, 105·1, 110·8, 115·9, 120·9, 121·3, 126·9, 127·3, 127·6, 128·4, 131·2, 137·2, 149·2, 153·8, 156·5, 167·5.

(−)-(4S)-2-(5′-Benzyloxy-1′,4′-dimethoxy-2′-naphthyl)-4-isopropyl-4,5-dihydrooxazole (3)

To a solution of the amide (10) (620 mg, 1·5 mmol) in dry dichloroethane (20 ml) at 0°C was added by syringe a solution of triethyloxonium tetrafluoroborate in dichloroethane (2 M, 1·8 ml). This was then allowed to stir overnight at 0°C, a procedure which resulted in a yellow precipitate. To this suspension was added (*S*)-valinol (400 mg, 3·9 mmol) and the

mixture was allowed to warm to room temperature and then heated under reflux for 11 h. The reaction mixture was cooled and washed with 5% Na_2CO_3, water, saturated NaCl, then dried ($MgSO_4$) and concentrated under reduced pressure to give a crude yellow oil which was flash chromatographed on silica gel by using 40% EtOAc/petrol as eluent. Recrystallization from petrol afforded the *oxazoline* (3) (473 mg, 64%) as pale yellow needles, m.p. 77–78°, $[\alpha]_D^{19}$ −43·5° (*c*, 1·8 in $CHCl_3$) (Found: C, 74·1; H, 6·6; N, 3·5. $C_{25}H_{27}NO_4$ requires C, 74·1; H, 6·7; N, 3·5%). ^{1}H n.m.r. δ 0·99, d, *J* 6·7 Hz, 3H, CH(C**H**$_3$)$_2$; 1·09, d, *J* 6·7 Hz, 3H, CH(C**H**$_3$)$_2$; 1·95, m, C**H**(CH$_3$)$_2$; 3·94, s, OMe; 3·97, s, OMe; 4·20, m, 2H; 4·49, m, 1H; 5·21, s, PhC**H**$_2$O; 7·02, d, *J* 7·8 Hz, 1H, ArH; 7·22, s, H3′; 7·30–7·60, m, 6H, ArH; 7·87, d, *J* 8·4 Hz, 1H, ArH. ^{13}C n.m.r. δ 18·2, 19·0, 32·9, 56·5, 62·7, 70·0, 71·6, 72·6, 106·0, 110·7, 116·4, 116·9, 126·9, 127·5, 128·3, 132·1, 137·4, 150·0, 153·0, 156·2, 162·2.

2-(5′-Benzyloxy-2′-bromophenyl)-1,3-dioxolan (4)

A solution of the bromide (11)[9] (2·87 g, 9·8 mmol), ethylene glycol (0·75 g, 12·1 mmol) and toluene-*p*-sulfonic acid (34 mg) in toluene (70 ml) was heated under reflux on a Dean–Stark apparatus for 20 h. The solution was cooled, washed with saturated $NaHCO_3$, water and brine, and dried over $MgSO_4$. Concentration under reduced pressure and recrystallization of the residue from ether/hexane afforded the *acetal* (4) (3·08 g, 93%) as colourless needles, m.p. 48–48·5° (Found: C, 57·5; H, 4·5; Br, 23·8. $C_{16}H_{15}BrO_3$ requires C, 57·4; H, 4·5; Br, 23·9%). ^{1}H n.m.r. δ 4·03–4·15, m, 4H; 5·05, s, PhC**H**$_2$O; 6·05, s, 1H, H2; 6·85, dd, *J* 8·4, 3·0 Hz, H4′; 7·24, d, *J* 3·0 Hz, H6′; 7·24–7·46, m, 6H, ArH. ^{13}C n.m.r. δ 65·4, 70·3, 102·4, 113·4, 114·3, 117·3, 127·5, 128·1, 128·6, 133·7, 136·5, 137·6, 158·1.

(+)-(R,4S)-2-[5′-Benzyloxy-1′-[4″-benzyloxy-2″-(1‴,3‴-dioxolan-2‴-yl)phenyl]-4′-methoxy-2′-naphthyl]-4-isopropyl-3-methyl-4,5-dihydrooxazolium Iodide (13)

A solution of dibromoethane (0·16 ml, 1·9 mmol) in tetrahydrofuran (2·3 ml) was added dropwise to a boiling mixture of the bromide (4) (630 mg, 1·9 mmol) and magnesium turnings (90 mg, 3·8 mmol) in tetrahydrofuran (2·3 ml). The solution was heated under reflux for 1 h, then cooled to room temperature and a solution of the oxazoline (3) (310 mg, 0·75 mmol) in tetrahydrofuran (3 ml) was added by means of a cannula. The solution was heated under reflux for 8 h, cooled, washed with saturated NH_4Cl, water and saturated NaCl, then dried and concentrated under reduced pressure to give the crude product which was purified by flash chromatography with 30% EtOAc/petrol as eluent to afford the minor isomer (12) (29 mg, 6%) as a yellow gum. ^{1}H n.m.r. δ 0·81, d, *J* 6·9 Hz, 3H, CH(C**H**$_3$)$_2$; 0·90, d, *J* 6·6 Hz, 3H, CH(C**H**$_3$)$_2$; 1·63, m, 1H, C**H**(CH$_3$)$_2$; 3·60–4·07, m, 7H; 4·04, s, OMe; 5·16, s, 2H, PhC**H**$_2$O; 5·22, s, 2H, PhC**H**$_2$O; 5·37, s, 1H, acetal H; 6·97–7·06, m, 3H, ArH; 7·24–7·51, m, 13H, ArH; 7·62, br d, *J* 7·2 Hz, 1H, ArH. ^{13}C n.m.r. δ 18·2, 19·0, 32·7, 56·1, 65·1, 65·2, 70·0, 70·5, 71·7, 72·5, 101·5, 105·7, 109·8, 111·7, 115·4, 118·8, 121·3, 126·6, 126·7, 127·0, 127·5, 127·6, 127·9, 128·3, 128·5, 129·8, 131·6, 131·9, 137·1, 137·2, 137·5, 138·4, 156·0, 156·5, 158·3, 164·5.

Further elution gave the major isomer (5) as a yellow gum (300 mg, 64%), ^{1}H n.m.r. δ 0·77, d, *J* 6·6 Hz, 3H, CH(C**H**$_3$)$_2$; 0·85, d, *J* 6·6 Hz, 3H, CH(C**H**$_3$)$_2$; 1·62, m, 1H, C**H**(CH$_3$)$_2$; 3·64–4·04, m, 6H; 4·04, s, OMe; 4·13, dd, *J* 9·6, 8·1 Hz, 1H; 5·15, s, 2H, PhC**H**$_2$O; 5·22, s, 2H, PhC**H**$_2$O; 5·30, s, 1H, acetal H; 6·97–7·63, m, 17H, ArH. ^{13}C n.m.r. δ 18·2, 18·9, 32·6, 56·1, 65·1, 65·2, 70·1, 70·4, 71·7, 72·5, 101·5, 105·6, 109·8, 111·9, 115·3, 118·8, 121·2, 126·7, 126·9, 127·0, 127·5, 127·6, 127·9, 128·3, 128·5, 129·6, 131·6, 132·4, 137·1, 137·2, 137·5, 138·0, 156·0, 156·6, 158·4, 164·7.

A solution of major isomer (5) (295 mg, 0·47 mmol) in dry acetonitrile (6 ml) and methyl iodide (0·3 ml) was stirred overnight at 60°C, then cooled and concentrated to give an orange gum. Trituration with ether, followed by recrystallization of the residue from acetone/ether yielded the *salt* (13) as pale yellow needles (212 mg, 59%), m.p. 218·5–222° (dec.), $[\alpha]_D^{19}$ +29·6° (*c*, 1·18 in $CHCl_3$) (Found: C, 63·1; H, 5·4; N, 1·8. $C_{41}H_{42}INO_6.0{\cdot}5H_2O$ requires C, 63·1; H, 5·6; N, 1·8%). ^{1}H n.m.r. δ 0·27, d, *J* 6·9 Hz, 3H, CH(C**H**$_3$)$_2$; 0·80, d, *J* 6·9 Hz, 3H, CH(C**H**$_3$)$_2$; 2·07, m, C**H**(CH$_3$)$_2$; 3·19, s, NMe; 3·69, m, 1H; 3·79, m, 1H; 3·92–4·02, m, 2H; 4·17, s, OMe; 4·44, dd, *J* 8·0, 8·4 Hz, 1H; 5·08, m, 1H; 5·13, s, PhC**H**$_2$O; 5·18, s, acetal H; 5·22, s, PhC**H**$_2$O; 5·35, dd, *J* 11·1, 9·3 Hz, 1H; 6·91, d, *J* 8·7 Hz, 1H, ArH; 7·06–7·08, m, 3H, ArH; 7·35–7·59, m, 12H, ArH; 8·00, s, 1H, ArH. ^{13}C n.m.r. δ 14·1,

17·7, 26·2, 34·7, 57·8, 61·6, 65·3, 65·4, 68·7, 70·2, 71·6, 72·5, 100·6, 104·7, 111·2, 113·5, 116·3, 119·2, 119·7, 120·3, 126·8, 127·6, 127·7, 128·1, 128·2, 128·4, 128·7, 131·8, 136·3, 136·5, 136·9, 139·3, 156·5, 158·3, 159·6, 174·2.

Crystallography

Crystal Data

$C_{41}H_{42}INO_6.0{\cdot}5H_2O$, M 780·70, orthorhombic, space group $P2_12_12_1$ (No. 19), a 9·943(2), b 19·319(2), c 20·052(2) Å, V 3851·8(10) Å^3, F(000) 1604, Z 4, D_c 1·346 g cm^{-3}, Cu K$\bar{\alpha}$ (nickel filtered) λ 1·5418 Å, μ 69·1 cm^{-1}, T 293(1) K.

Structure Determination

The crystal selected was a colourless needle of approximate dimensions 0·35 by 0·16 by 0·16 mm. Accurate unit cell parameters were obtained by a least-squares procedure from the setting angles of 25 reflections. Intensity data were collected by using an Enraf–Nonius CAD-4MachS single-crystal X-ray diffractometer according to the $\omega:2\theta$ scan method. A total of 5509 reflections were measured, $4 \leq 2\theta \leq 150°$, of which 5262 were unique (R_{int} 0·022), and 3415 having $I \geq 2\sigma(I)$. Three intensity control reflections, monitored every 9600 s of X-ray exposure time, showed no significant variation in intensity. Corrections were applied for Lorentz and polarization effects, but not for extinction. Analytical absorption corrections were applied, the maximum and minimum transmission factors being 0·502 and 0·313, respectively.

The structure was solved by using a combination of direct methods and difference synthesis,[13,14] and refined with a full-matrix least-squares refinement procedure. All hydrogen atom sites were found on a difference electron-density map, except for those on the water molecule; all were included at calculated positions and refined, the riding model being used. Final refinement, on F^2 and by using all data, was carried out with anisotropic displacement factors applied to each of the non-hydrogen atoms, isotropic for the hydrogen atoms and with a weighting scheme of type $1/[\sigma^2(F_o^2)+(0{\cdot}0678P)^2+2{\cdot}5207P^2]$, where $P = (F_o^2+2F_c^2)/3$. The function minimized was $\Sigma w(F_o^2-F_c^2)^2$. At convergence, R_1 $[I \geq 2\sigma(I)]$ 0·0508 and wR_2 (all data) 0·1465, where $R_1 = \Sigma||F_o| - |F_c||/\Sigma F_o$ and $wR_2 = [\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$. In the final difference map, the maximum peak height was 0·45 e Å^{-3}, close to the iodine atom. The Flack absolute structure factor[15] refined to 0·012(8), giving an absolute configuration consistent with the known chirality around C(4‴). An analysis of variance showed no unusual features.

Final atomic coordinates are given in Table 1. The atomic scattering factors of C, H, I, N and O were those incorporated in the SHELXL-93 program system,[14] obtained from International Tables Vol. C;[16] corrections were made for anomalous dispersion. Calculations were carried out on a Vaxstation 4000 VLC computer system. Fig. 3 was prepared from the output of ORTEPII.[17] Material deposited* includes complete geometry, hydrogen atom positions, anisotropic displacement parameters, and a listing of the final observed and calculated structure factors.

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* Copies are available on application to the Australian Journal of Chemistry, P.O. Box 89, East Melbourne, Vic. 3002.

[13] Sheldrick, G. M., SHELXS86, 'Program for Crystal Structure Solution', *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
[14] Sheldrick, G. M., SHELXL-93. 'Program for Crystal Structure Refinement', University of Göttingen, Germany, 1993.
[15] Flack, H. D., *Acta Crystallogr., Sect. C*, 1983, **39**, 876.
[16] 'International Tables for X-Ray Crystallography' Vol. C, p. 219 (Kluwer: Dordrecht, The Netherlands, 1993).
[17] Johnson, C. K., ORTEPII, 'Fortran Thermal Ellipsoid Plot Program 1976', Report ORNL-5138, Oak Ridge National Laboratories, Tennessee, U.S.A.