Synthesis of Steroidal Cyclodimers from Cholic Acid; a Molecular Framework with Potential for Recognition and Catalysis

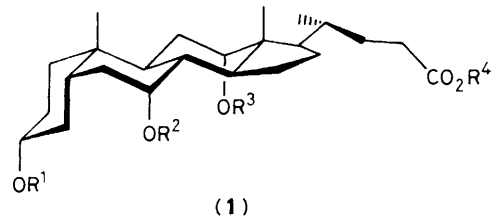
Richard P. Bonar-Law and Anthony P. Davis*

Department of Chemistry, Trinity College, Dublin 2, Ireland

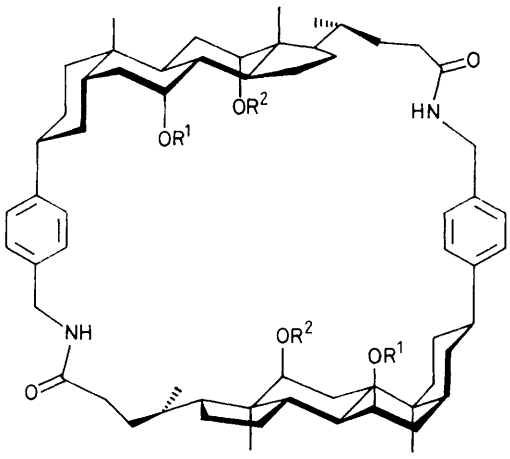
Macrocycles (**2a**—**f**) were synthesized from cholic acid (**1a**) in up to 33% overall yield; the 'cholaphane' framework on which they are based has substantial potential variability and should prove useful in biomimetic chemistry.

A general feature of enzymes, arguably responsible for much of their catalytic power and selectivity, is their ability to surround their substrates with various precisely positioned functional groups. In order to mimic enzyme action, it is thus desirable to have access to molecular frameworks which can surround small molecules, are fairly rigid, carry controllable functionality and are reasonably easy to assemble. The steroid nucleus appears attractive as a component of such frameworks as it is large, rigid, chiral, and (unlike comparable aromatic nuclei) composed of sp^3 carbon atoms which allow a choice of two substituent orientations at each position. Cholic acid (**1a**) has particular advantages; it is inexpensive, chemically well studied, bears a useful array of differentiable functionality (*vide infra*), and has a curved profile which lends itself to incorporation in a macrocyclic structure.

We wish to report practical and high-yielding transformations of (**1a**) into 'cholaphanes' (**2a**—**f**). We suggest that the framework common to these molecules may prove a



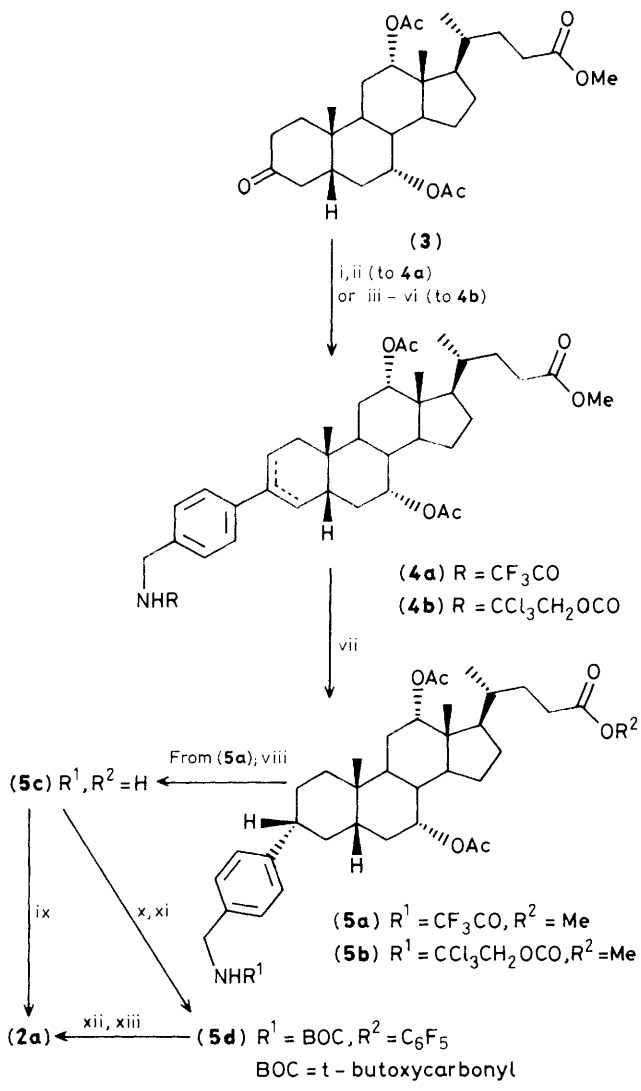
(1)



(2)

(1) a; R^1, R^2, R^3, R^4 = H
b; R^1, R^2, R^3 = H, R^4 = Me
c; R^1, R^2, R^3 = Ac, R^4 = Me
d; R^1, R^2 = Ac, R^3 = H, R^4 = Me
e; R^1 = H, R^2, R^3 = Ac, R^4 = Me

(2) a; R^1, R^2 = Ac
b; R^1, R^2 = PhCO
c; R^1 = Ac, R^2 = $PhCH_2$
d; R^1 = H, R^2 = $PhCH_2$
e; R^1 = Ac, R^2 = H
f; R^1, R^2 = H



Scheme 1. *Reagents and conditions*: i, $(Me_3Si)_2NCH_2$-*p*-C_6H_4-Li, MnI_2, Et_2O; ii, $(CF_3CO)_2O$, CF_3CO_2H; iii, $(CF_3SO_2)_2O$, 2,6-di-t-butyl-4-methylpyridine; iv, $(Me_3Si)_2NCH_2$-*p*-C_6H_4-ZnBr, $Pd(PPh_3)_4$, tetrahydrofuran (THF), Et_2O; v, $ZnBr_2$, MeOH; vi, CCl_3CH_2OCOCl, K_2CO_3; vii, H_2, Pd/C; viii, NaOH, MeOH, THF; ix, $(EtO)_2POCN$, $CHCl_3$, dimethylformamide (DMF), K_2HPO_4, [substrate] = 10 mM; x, $(BOC)_2O$, $EtPr^i_2N$, THF; xi, dicyclohexylcarbodiimide (DCC), C_6F_5OH; xii, CF_3CO_2H; xiii, DMAP·HO_2CCF_3, $CHCl_3$, DMF, K_2HPO_4, [substrate] = 1.4 mM.

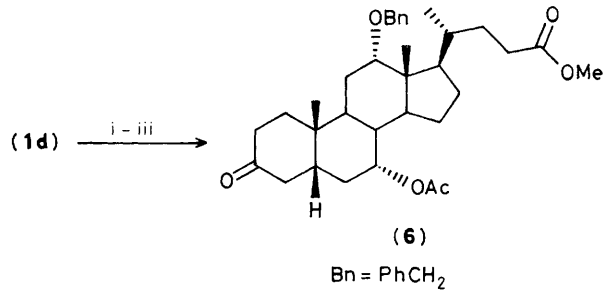
valuable design tool in biomimetic chemistry, particularly because of the controllability of its substitution pattern. Linear steroidal dimers capable of biomimetic catalysis have been described by Guthrie and co-workers,[1] and two groups have reported complexation studies involving linear dimers of cholic acid.[2]

The methodology used in the syntheses of (**2a—f**) is exemplified in Scheme 1. The starting ketone (**3**)[3] was prepared in 89% yield from cholic acid *via* conversion to methyl cholate (**1b**) (MeOH, AcCl), tri-acetylation giving (**1c**) [Ac_2O, pyridine, dimethylaminopyridine (DMAP)], de-acetylation at the 3-position to give (**1e**) (MeOH, AcCl),[4] and oxidation (pyridinium chlorochromate). The introduction of the 4-(aminomethyl)phenyl unit in the 3-α position was accomplished in two ways. The first relied on the selectivity of organomanganese reagents for ketones over esters.[5] Thus, treatment of (**3**) with the organomanganese reagent derived from *N*,*N*-bis(trimethylsilyl)-*p*-bromobenzylamine† gave a mixture of alcohols which were dehydrated, desilylated and trifluoroacetylated to give alkenes (**4a**) (principally the $\Delta^{3,4}$ isomer). Hydrogenation of (**4a**) occurred on the convex β-face to give (**5a**)‡ in 75% overall yield from (**3**).

In the second, treatment of ketone (**3**) with trifluoromethanesulphonic anhydride and 2,6-di-t-butyl-4-methylpyridine yielded a mixture of enol triflates which were coupled with *p*-(bistrimethylsilylamino)methylphenylzinc bromide in

† The *N*-protected *p*-bromobenzylamine was prepared from *p*-bromobenzyl bromide and $NaN(SiMe_3)_2$, according to the method of Bestmann.[6] *N*,*N*-Bis-trimethylsilyl protection had previously been used in metallated aniline derivatives.[7]

‡ The stereochemistry of hydrogenation was determined initially by the ^1H n.m.r. spectroscopy chemical shift of the C(3)–H in (**5a**) and (**5b**); δ ($CDCl_3$, 80 MHz) 2.5 (3β-H), compared to 3.0 (3α-H in analogous model compounds). Confirmation was provided by the C(3)–H coupling pattern in the 400 MHz ^1H n.m.r. spectrum of macrocycle (**2a**) (*vide infra*).



Scheme 2. *Reagents and conditions*: i, $PhCH_2OC(NH)CCl_3$, CF_3SO_3H cat.; ii, MeOH, HCl; iii, py·$CrCl_2O_2$ (py = pyridine).

the presence of $Pd(PPh_3)_4$.§ Desilylation followed by protection with CCl_3CH_2OCOCl and K_2CO_3 gave (**4b**) which was hydrogenated to (**5b**). In the example shown this method gave modest yields, mainly because of the reaction of the acetyl protecting groups with the triflic anhydride. However, it proved useful in other cases including the precursor of the benzoyloxy-substituted cholaphane (**2b**).

Deprotection of the carboxyl and amino groups in (**5a**) gave a 90% yield of amino-acid (**5c**) which, on treatment with diethyl cyanophosphate, cyclodimerised directly to (**2a**) in 32% crystalline yield. Alternatively, a 55% yield of (**2a**) from (**5c**) could be obtained by a rather more laborious method involving the pentafluorophenyl ester (**5d**).[9] Both methods feature the use of K_2HPO_4 as an acid scavenger which is insoluble in the reaction medium.[10] Notably, the former method does not require extremely high dilution but takes place at 10 mM substrate concentration.

Taking the most successful methods at each stage, the overall yield of (**2a**) from cholic acid is calculated to be 33%. The cholaphane framework can thus be assembled with sufficient efficiency to be a realistic starting point for further investigations.

Although the inward-directed functional groups in (**2a**) are all the same, it is easy to arrange for them to be differentiated. Thus, methyl cholate (**1b**) can be selectively diacetylated to give (**1d**) (pyridine, Ac_2O)[11] which is easily converted to ketone (**6**) (Scheme 2) and then to cholaphane (**2c**). Furthermore, cholaphanes (**2a,b**) have been synthesised *via* stepwise cyclodimerisations involving linear dimers. This methodology should be readily adaptable to the construction of cholaphanes bearing four different functional groups.

Removal of the acetyl groups in (**2a**) gave the tetrahydroxycholaphane (**2f**) (90% yield), while similar treatment of (**2c**) gave the dibenzyloxydihydroxycholaphane (**2d**). Complementary deprotection of (**2c**) was possible by hydrogenolysis, leading to the diacetoxydihydroxycholaphane (**2e**).

All the cholaphanes were isolated as solvated crystalline solids with ^{1}H n.m.r.¶ spectra consistent with their structures. Microanalyses have been obtained for (**2a**),¶ (**2b**), and (**2f**), and (**2c—e**) have been converted to (**2f**). ^{13}C n.mr. spectra¶ have been obtained for (**2a—e**) and m.s. for (**2a**) [electron impact; *m/z* 1007 (M^+ − 2AcOH), 947 (M^+ − 3AcOH)] and (**2f**) [fast atom bombardment (f.a.b.); *m/z* 960 (MH^+)]. Cholaphane (**2a**) is currently being subjected to *X*-ray crystallographic analysis. The dihydroxycholaphanes (**2d,e**) should be useful precursors of cholaphanes with other functionalities, and cholaphane (**2f**), with its four inward-directed hydroxy groups, may prove to have interesting complexation properties.

We wish to thank EOLAS, the Irish Science and Technology Agency, for financial support, Professor M. T. Reetz for assistance in obtaining high field n.m.r. spectra and Dr. J. K. M. Sanders for mass spectra.

Received, 9th December 1988; Com. 8/04868A

References

1 J. P. Guthrie, J. Cossar, and B. A. Dawson, *Can. J. Chem.*, 1986, **64**, 2456; J. P. Guthrie, P. A. Cullimore, R. S. McDonald, and S. O'Leary, *Can. J. Chem.*, 1982, **60**, 747.
2 J. McKenna, J. M. McKenna, and D. W. Thornthwaite, *J. Chem. Soc., Chem. Commun.*, 1977, 809; C. J. Burrows and R. A. Sauter, *J. Inclusion Phenomena*, 1987, **5**, 117.
3 A. S. Jones, M. Webb, and F. Smith, *J. Chem. Soc.*, 1949, 2164.
4 J. R. Dias and R. Ramachandra, *Synth. Commun.*, 1977, **7**, 293.
5 G. Cahiez and J. F. Normant, *Tetrahedron Lett.*, 1977, 3383.
6 H. J. Bestmann and G. Wölfel, *Chem. Ber.*, 1984, **117**, 1250.
7 D. R. M. Walton, *J. Chem. Soc. (C)*, 1966, 1766; W. Broser and W. Harrer, *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 1081.
8 R. McCague, *Tetrahedron Lett.*, 1987, **28**, 701.
9 M. Bodanszky in 'The Peptides,' vol. 1, eds. E. Gross and J. Meienhofer, Academic Press, New York, 1979, p. 106.
10 *cf.* S. F. Brady, R. M. Freidinger, W. J. Paleveda, C. D. Colton, C. F. Homnick, W. L. Whitter, P. Curley, R. F. Nutt, and D. F. Veber, *J. Org. Chem.*, 1987, **52**, 764.
11 L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, 1950, **72**, 5530.
12 J. W. Blunt and J. B. Stothers, *Org. Magn. Reson.*, 1977, **9**, 439.

§ Essentially similar methodology was developed independently by McCague for the synthesis of certain 1,1-diarylethenes.[8]

¶ *Spectroscopic data* for (**2a**); ^{1}H n.m.r. δ ($CDCl_3$, 400 MHz) 7.18 (4H, d, *J* 8 Hz, Ar–H), 7.15 (4H, d, *J* 8 Hz, Ar–H), 5.85 (2H, dd, *J* 7.5, 4 Hz, NH), 5.1 (2H, t, *J* 3 Hz, 12β-H), 4.92 (2H, q, *J* 3.3 Hz, 7β-H), 4.77 (2H, dd, *J* 14.95, 7.55 Hz, N–CH), 4.07 (2H, dd, *J* 14.95, 3.95 Hz, N–CH), 2.44 (2H, tt, *J* 12, 3.5 Hz, 3β-H), 2.033 (s, OAc), 2.026 (s, OAc), 0.93 (s, 19 Me), 0.76 (s, 18 Me); ^{13}C n.m.r. δ ($CDCl_3$) 173.3 [C(24)], 170.0 (O*C*OMe), 169.8 (O*C*OMe), 146.8 (Ar), 136.2 (Ar), 127.4 (Ar), 126.7 (Ar), 75.8 [C(12)], 71.0 [C(7)], 46.5 [C(17)], 45.0 [C(13)], 44.4 [C(14)], 44.0 [C(3)], 42.8 (*C*H_2N), 42.5 [C(5)], 37.5 [C(8)], 37.0 [C(1)], 35.8 [C(4)], 35.0 [C(20)], 34.0 [C(10)], 33.2, 32.4 [C(22), C(23)], 31.3 [C(6)], 29.8 [C(2)], 29.5 [C(9)], 27.6 [C(16)], 25.7 [C(11)], 23.0 [C(19)], 22.8 [C(15)], 21.6 (OCO*Me*), 21.2 (OCO*Me*), 17.4 [C(21), 12.1 [C(18)] (assignments by DEPT, H-C COSY and literature comparison[12]); ν_{max} ($CHCl_3$) 3450 (NH), 1720 (Ac), 1660 (-CONH-) cm^{-1}; satisfactory elemental analyses were obtained.