Cholic Acid Derived Novel Chiral Auxiliaries for Asymmetric Diels–Alder Reactions†

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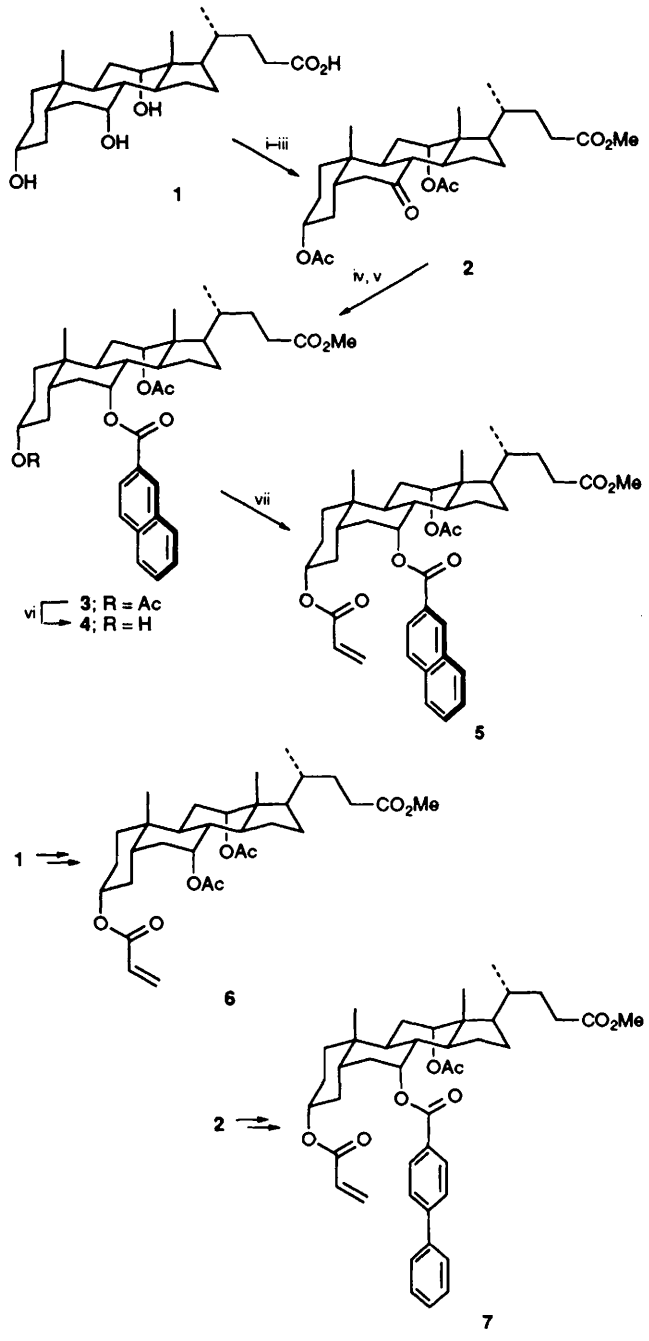
Cholic acid-based chiral acrylate **5** yields a Diels–Alder adduct with cyclopentadiene in the presence of $BF_3{\cdot}OEt_2$ with 88% diastereoselectivity.

The Diels–Alder reaction is one of the most important reactions for multiple carbon–carbon bond formation with a high degree of stereocontrol. A vast amount of work has been carried out during the past three decades on asymmetric Diels–Alder reactions.[1] Numerous chiral auxiliaries,[2] and catalytic methods[3] have been reported for [4 + 2] cycloaddition reactions with varying degrees of success. Surprisingly, one of the most abundant sources of chirality, the bile acids, have not been used as chiral auxiliaries for cycloaddition processes.[4] We have recently described a novel asymmetric synthesis of the Tröger's base unit using 7-deoxycholic acid as

† Bile acids in Asymmetric Synthesis, Part 2. For Part 1, see ref. 5.



Scheme 1. *Reagents and conditions*: i, MeOH–HCl, reflux (15 min), 95%; ii, *N*-bromosuccinimide (1.25 equiv.), acetone–H_2O, room temp., 24 h, 64%; iii, Et_3N–dimethylaminopyridine–Ac_2O, room temp., 24 h, 90%; iv, $NaBH_4$, MeOH, 0 °C, 1 h, 83%; v, CaH_2, Bu^n_4NI, 2-naphthoyl chloride, toluene, reflux, 24 h, 86%; vi, anhyd. K_2CO_3, MeOH, room temp., 5 h, 90%; vii, Et_3N, CH_2Cl_2, acryloyl chloride, 0 °C, 1 h, 87%

a chiral template.[5] We now report Diels–Alder reactions using cholic acid derived chiral acrylates **5–7**.

The 3α and 7α hydroxys of cholic acid have a 1,5 relationship, but because of the *cis*-fused *A/B* ring junction they are quite close (*ca.* 5 Å) to each other. It seemed to us that the attachment of a large and flat aromatic surface to the 7α OH group would hinder one face of a double bond suitably attached to the 3α OH. Accordingly, compound **5** was designed to test our hypothesis.

Commercially available cholic acid **1** was converted in three steps to the known 7-oxo-3α,12α-diacetate **2**.[6] Reduction of **2** followed by esterification under Oppenauer conditions[7] with

Table 1 Lewis acid catalysed and uncatalysed Diels–Alder reactions of steroidal acrylates with cyclopentadiene in CH_2Cl_2

Entry	Substrate	Lewis acid (equiv.)	*T*/°C	*t*/h	Yield (%)	*Endo*:*exo*[a]	D.e./% (config.)[b]
1	**6**	BF_3·OEt_2 (4.0)	−40	12	60	—[c]	2(*S*)
2	**6**	Uncat.	0	48	80	—[c]	3(*S*)
3	**5**	Uncat.	0	36	90	79:21	36(*R*)
4	**5**	BF_3·OEt_2 (5.0)	−40	7	86	98:2	73(*S*)
5	**5**	BF_3·OEt_2 (1.0)	−80	12	87	99:1	79(*S*)
6	**5**	BF_3·OEt_2 (5.1)	−80	7	91	99:1	88(*S*)
7	**5**	$AlCl_3$ (4.9)	−80	9	90	98:2	74(*S*)
8	**5**	$SnCl_4$ (1.7)	−40	12	76	97:3	44(*S*)
9	**7**	BF_3·OEt_2 (4.9)	−40	8	93	98:2	64(*S*)

[a] *Endo*:*exo* ratios were calculated by HPLC data. [b] D.e. were calculated from ^1H NMR and HPLC data. The configuration refers to the stereochemistry of C-2 of the bicyclo[2.2.1] system. [c] Not determined.

2-naphthoyl chloride gave compound **3**, which was selectively deacetylated and esterified to give acrylate **5** (Scheme 1). Compound **6** was synthesized in four steps from cholic acid as a control. Compound **7** was also synthesised in a manner analogous to **5**. The results of the Diels–Alder reactions carried out in CH_2Cl_2 are summarized in Table 1.‡,§

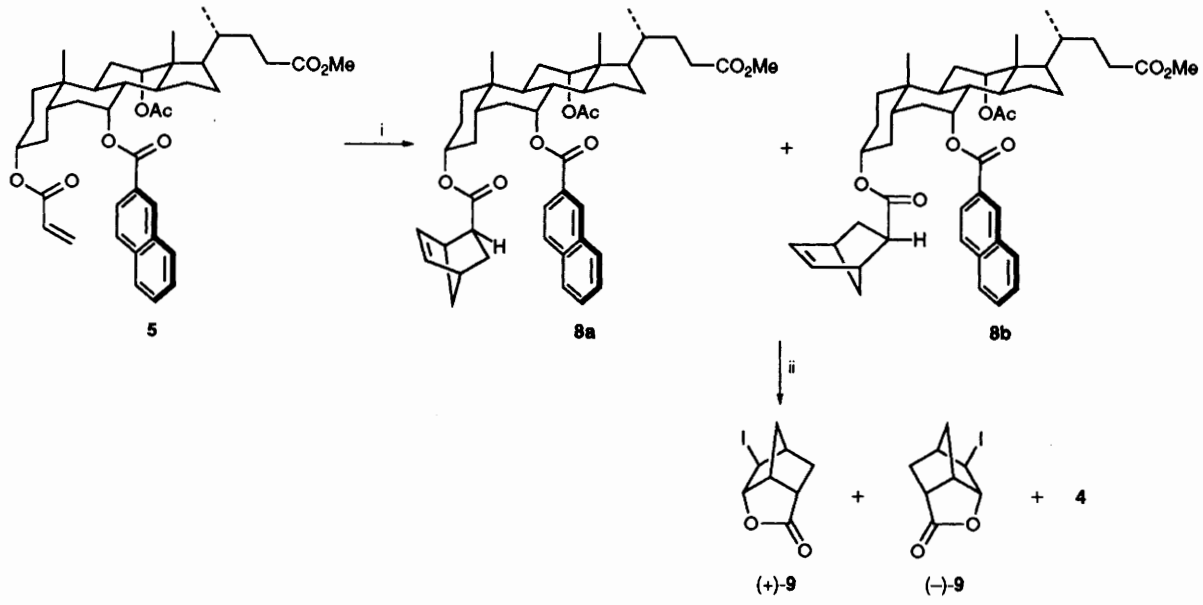
It is noteworthy that in the absence of the naphthalene unit attached at C-7 (compound **6**) there is no stereoselection either in the uncatalysed or in the catalysed rection. The uncatalysed reaction on **5** yielded a diastereoisomeric mixture of **8a** and **8b** [36% diastereoisomeric excess (d.e.), **8b** in excess]. Lewis acid catalysis at low temperature was examined with various Lewis acids. The results show that BF_3·OEt_2 is the most effective Lewis acid at −80 °C, yielding exclusively (>99%) the *endo* product with 88% d.e. in favour of **8a**. Our preliminary results show that a biphenyl-4-carboxylate ester **7** at C-7 is not as effective as the 2-naphthoate ester.

Since attempts to selectively remove the bicyclo[2.2.1] adduct from the chiral auxiliary under a variety of basic conditions were unsuccessful, iodolactonization was attempted.[8] Treatment of a CH_2Cl_2 solution of **8a** and **8b** with

‡ Authentic samples of the cycloaddition products were synthesized from the racemic as well as scalemic (40% e.e., 2*R*) samples of *endo*-norborn-5-ene-2-carboxylic acid and compound **4**. NMR spectra (400 MHz) and HPLC traces (ODS column, 90/10 MeOH–H_2O) of these samples were recorded and compared with those of the reaction products. We thank Professor M. Nakazaki (Japan) for providing the scalemic sample to us.

§ *Selected spectroscopic data*: for **5** m.p. 173 °C; $[\alpha]_D^{25}$ + 99.4 (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.619 (s, 1 H, naphthoate α-H), 6.165 (dd, *J* 17.3 and 1.5 Hz, 1 H, *cis H*-CH=CH-CO), 5.917 (dd, *J* 17.3 and 10.4 Hz, 1 H, CH_2=C*H*-CO), 5.606 (dd, *J* 10.4 and 1.5 Hz, 1 H, *trans H*-CH=CH-CO), 5.29 (br s, 1 H, 7-H), 5.17 (br s, 1 H, 12-H), 4.66 (m, 1 H, 3-H), 3.60 (s, 3 H, $COOCH_3$), 2.193 (s, 3 H, 12-$OCOCH_3$), 1.008 (s, 3 H, 19-CH_3), 0.815 (d, *J* 6.5 Hz, 3 H, 21-CH_3) and 0.772 (s, 3 H, 18-CH_3); MS (70 eV): *m/z* 672 (M^+, 17%), 440 (58%), 253 (88%), 172 (100%).

8a: m.p. 141 °C; $[\alpha]_D^{25}$ + 42.9 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1 H, naphthoate α-H), 5.78 [m, 1 H, 3-(6′-H)], 5.71 [m, 1 H, 3-(5′-H)], 5.26 (s, 1 H, 7-H), 5.18 (s, 1 H, 12-H), 4.50 (m, 1 H, 3-H), 3.604 (s, 3 H, $COOCH_3$), 3.00 [s, 1 H, 3-(2′-H)], 2.224 (s, 3 H, 12-$OCOCH_3$), 0.988 (s, 3 H, 19-CH_3), 0.826 (d, *J* 6.5 Hz, 3 H, 21-CH_3) and 0.773 (s, 3 H, 18-CH_3); MS (70 eV): *m/z* 738 (M^+, 1%), 672 ($M^+ - C_5H_6$, 6%), 440 (35%), 253 (75%), 172 (70%), 155 (100%).



Scheme 2. *Reagents and conditions*: i, cyclopentadiene–$CHCl_2$, Lewis acid, molecular sieve 4A; ii, CH_2Cl_2–$NaHCO_3$ $(aq)_g$, I_2–KI, room temp., 2 h

I_2–KI–$NaHCO_3$ (aq.) afforded enantiomeric iodolactones (+)-**9**/(−)-**9** in 75% yield; the chiral auxiliary **4** was recovered in 88% yield (Scheme 2). To the best of our knowledge, this is the first application of iodolactonization in the removal of a Diels–Alder adduct from a chiral auxiliary. The enantiomeric excess (e.e.) of the (+)-**9**/(−)-**9** mixture was found to be in good agreement with the observed d.e. of **8a**/**8b**.[9]

In conclusion, we have developed a novel chiral auxiliary for the Diels–Alder reaction using readily available and inexpensive cholic acid. We believe that a similar strategy would be useful for carrying out other types of reactions such as 1,4-conjugate addition, osmylation *etc.* These investigations are in progress.

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References

1 W. Oppolzer, in *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, p. 315.
2 L. A. Paquette, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1984, vol. 3, p. 455; W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 876; *Tetrahedron*, 1987, **43**, 1969; G. Helmchen, R. Karge and J. Weetman, in *Modern Synthetic Methods*, ed. R. Scheffold, Springer Heidelberg, 1986, vol. 4, p. 262; E. J. Corey, *Pure Appl. Chem.*, 1990, **62**, 1209; D. A. Evans, K. T. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238; W. Stahle and H. Kunz *Syn Lett*, 1991, 260.
3 H. B. Hagan and O. Riant, *Chem. Rev.*, 1992, **92**, 1007; K. Narakasa, *Synthesis*, 1991, 1.
4 For a cholestanol derived chiral auxiliary, see; W. Oppolzer, M. Kurth, D. Reichlin, C. Chapuis, M. Mohnhauptand and F. Moffatt, *Helv. Chim. Acta*, 1981, **64**, 2802.
5 U. Maitra and B. G. Bag, *J. Org. Chem.*, 1992, **57**, 6979.
6 L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, 1949, **41**, 3935; 1950, **72**, 5530.
7 R. V. Oppenauer, *Monatsch. Chem.*, 1966, **97**, 62.
8 P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, 1978, **100**, 3950; for iodolactonization of norbornene caboxylic acid and its ester derivatives: see B. Giese, *Chem. Ber.*, 1977, **108**, 2978.
9 W. Kirmse and R. Siegfried, *J. Am. Chem. Soc.*, 1983, **105**, 950.