Nett Asymmetric Conjugate Addition of a Recyclable Acetic Ester Enolate Equivalent

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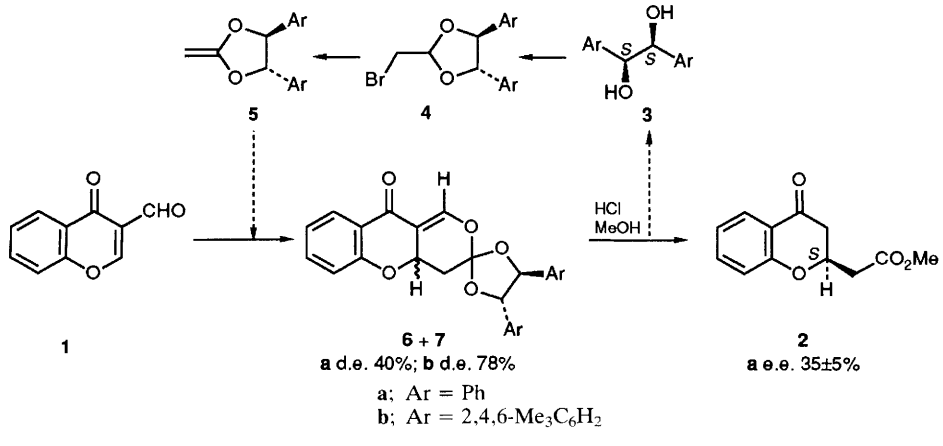
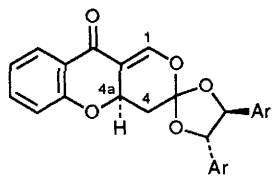
Heterodiene cycloadditions of 3-formyl chromone to ketene acetals derived from C_2-symmetric 1,2-diarylethane-1,2-diols are diastereoselective; methanolysis of the cycloadducts derived from (*S,S*)-hydrobenzoin releases optically enriched methyl 3,4-dihydro-4-oxo-2*H*-1-benzopyran-2-ylacetate and the optically pure 1,2-diol.

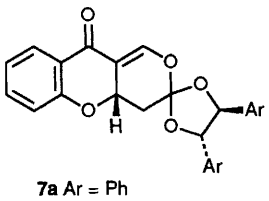
The asymmetric conjugate addition of an acetic ester enolate equivalent to an achiral α,β-unsaturated carbonyl function is a useful synthetic manoeuvre.[1] We describe herein the prototypes of a new variant of this process, based on the diastereoselective heterodiene cycloaddition of a C_2-symmetric ketene acetal to a formyl-activated enone and illustrated by



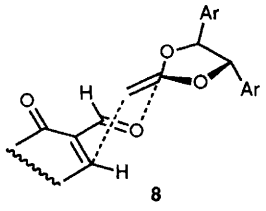
Scheme 1 d.e. = diastereoisomeric excess; e.e. = enantiomeric excess



6a Ar = Ph
6b Ar = 2,4,6-$Me_3C_6H_2$



7a Ar = Ph
7b Ar = 2,4,6-$Me_3C_6H_2$



8

the transformation of chromone-3-carbaldehyde **1** into the ester **2** (Scheme 1).† Acid-catalysed methanolysis of the products **6** and **7** induces transesterification and retro-Claisen deformylation, generating the product **2** and releasing the 1,2-diol from which the ketene acetal **5** can be regenerated.

Two racemic C_2-symmetric ketene acetals have been studied. Heating bromoacetaldehyde diethyl acetal with (±)-hydrobenzoin **3a** produced the bromoacetal (±)-**4a** (85%). Dehydrobromination of **4a** with potassium *tert*-butoxide (1 equiv.) in tetrahydrofuran (THF) at 25 °C for 1 h gave a solution of the ketene acetal (±)-**5a**, which was cooled to −78 °C, treated with the chromone **1** (1 equiv.) in THF, and allowed to reach room temperature overnight. Chromatography of the products over Florisil yielded unchanged **1** (15%), **4a** (9%), and the mixed cycloadducts **6a** and **7a** (61%; 7:3 by ^{1}H NMR spectroscopy), which were separated by HPLC. Treating the mixture of **6a** and **7a** with 3% methanolic HCl (reflux, 16 h), followed by flash chromatography over silica gel, gave the ester (±)-**2**[2] (60%) and (±)-hydrobenzoin **3a** (58%). A second sequence, starting with the diol (±)-**3b**[3] and with isolation[4] of the ketene acetal (±)-**5b**, gave the cycloadducts **6b** and **7b** (ratio 8.2:1).

The stereochemical assignments for **6** and **7** are based on the result obtained using (−)-hydrobenzoin (*S,S*)-**3a** as the auxiliary diol, the final product in this case being identified as the ester (*S*)-**2** (e.e, 35 ± 5%)‡ from its CD spectrum, which was complementary to that of (*S*)-2-methylchroman-4-one.[5] Analysis of the diol (*S,S*)-**3a** recovered at the end of this sequence indicated that no racemisation had occurred during its three-step cycle.‡

While the degree of concertedness of the above cycloaddition is unknown, the preferential formation of **6** is consistent with the mechanistic model depicted in **8**, in which the R-group on the reacting face of the ketene acetal can more easily avoid the approaching heterodiene.[6]

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References

1 For examples, see G. H. Posner, M. Weitzberg, T. G. Hamill, E. Asirvatham, H. Cun-Heng and J. Clardy, *Tetrahedron*, 1986, **42**, 2919; G. H. Posner, *Acc. Chem. Res.*, 1987, **20**, 72, and references cited therein.
2 S. J. Coutts and T. W. Wallace, *Tetrahedron Lett.*, 1987, **28**, 5195. For another route to esters of this type, see Y.-G. Lee, K. Ishimaru, H. Iwasaki, K.-Y. Ohkata and K. Akiba, *J. Org. Chem.*, 1991, **56**, 2058.
3 J. Souppe, L. Danon, J. L. Namy and H. B. Kagan, *J. Organomet. Chem.*, 1983, **250**, 227.
4 For the procedure, see W. J. Bailey and L.-L. Zhou, *Tetrahedron Lett.*, 1991, **32**, 1539.
5 S. T. Saengchantara and T. W. Wallace, *Tetrahedron*, 1990, **46**, 6553, and references cited therein.
6 For cycloadditions of related species, see U. Grusek and M. Heuschmann, *Tetrahedron Lett.*, 1987, **28**, 2681; J. P. Konopelski and M. A. Boehler, *J. Am. Chem. Soc.*, 1989, **111**, 4515.

† New compounds gave satisfactory spectroscopic and analytical data. *Selected data* (δ_H at 300 MHz unless indicated): **2**, 2.72 (1 H, dd, *J* 5.5, 16 Hz, α-H), 2.75–2.80 (2H, m, 3-H_2), 2.86 (1 H, dd, *J* 7, 16 Hz, α-H), 3.73 (3 H, s, OMe), 4.90 (1 H, m, 2-H); **4a**, 3.66 (2 H, d, *J* 3.5 Hz, $BrCH_2$), 4.81 (1 H, d, *J* 8 Hz, OC*H*Ph), 4.88 (1 H, d, *J* 8 Hz, OC*H*Ph), 5.69 (1 H, t, *J* 3.5 Hz, $BrCH_2CH$); (*S,S*)-**4a**, $[\alpha]_D^{23}$ −52° ±8° (*c* 1, CH_2Cl_2); **4b**, 2.09 (12 H, s, 2,6-ArMe), 2.18 (6 H, s, 4-ArMe), 3.60 (2 H, d *J* 4.7 Hz, $BrCH_2$), 5.52 (1 H, d, *J* 9.8 Hz, OC*H*Ar), 5.58 (1 H, d, *J* 9.8 Hz, OC*H*Ar), 5.70 (1 H, t, *J* 4.7 Hz, $BrCH_2CH$), 6.71 (4 H, s, ArH); **5b**, 2.1–2.2 (18 H, 3 × s, ArMe), 3.15 (2 H, s, CH_2=C), 5.74 (1 H, s, C*H*Ar), 6.76 (4 H, s, ArH); **6a**, (200 MHz) 5.03 (1 H, d, *J* 9 Hz, C*H*Ph), 5.37 (1 H, d, *J* 9 Hz, C*H*Ph), 5.40 (1 H, ddd, *J* 1.5, 7, 10.5 Hz, 4a-H), 7.70 (1 H, d, *J* 1.5 Hz, 1-H); **7a**, (200 MHz) 5.03 (1 H, d, *J* 9 Hz, C*H*Ph), 5.19 (1 H, d, *J* 9 Hz, C*H*Ph), 5.42 (1 H, ddd, *J* 1.5, 6.5, 11 Hz, 4a-H), 7.64 (1 H, d, *J* 1.5 Hz, 1-H); **6b**, 5.37 (1H, ddd, *J* 1.5, 6.5, 10.7 Hz, 4a-H), 5.78 (1 H, d, *J* 10.5 Hz, C*H*Ar), 6.03 (1 H, d, *J* 10.5 Hz, C*H*Ar), 7.64 (1 H, d, *J* 1.5 Hz, 1-H); **7b**, 5.37 (1 H, ddd, *J* 1.5, 6.5, 11.1 Hz, 4a-H), 5.79 (1 H, d, *J* 10.6 Hz, C*H*Ar), 5.90 (1 H, d, *J* 10.6 Hz, C*H*Ar), 7.61 (1 H, d, *J* 1.5 Hz, 1-H).

‡ Determined by analysis of the 300 MHz ^{1}H NMR spectrum in the presence of 4 equiv. of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

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