Pergamon

Tetrahedron Letters, Vol. 35, No. 40, pp. 7451-7454, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01559-7

Dispiroketals in Synthesis (Part 13)[1]: Functionalised Dispiroketals as New Chiral Auxiliaries; Highly Stereoselective Diels-Alder Reactions using a Bifunctional, C_2-Symmetrical Chiral Auxiliary.

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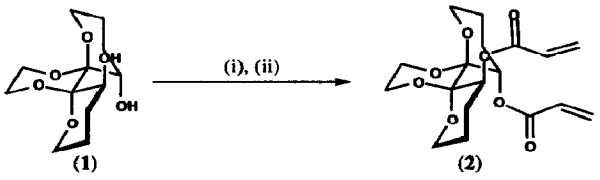
Abstract: Highly selective, asymmetric, Lewis acid catalysed Diels-Alder reactions are reported with a bifunctional, C_2-symmetrical diacrylate derivative obtained from a chiral auxiliary based on dihydroxylated dispiroketals.

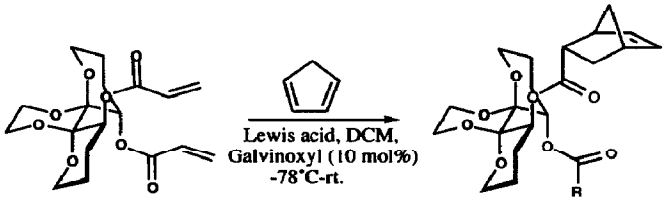
In the previous paper we reported the preparation of a C_2-symmetrical dihydroxylated dispiroketal (**1**) in optically pure form. Here we show that the corresponding diacrylate (**2**)[2] (Scheme 1) undergoes Lewis acid catalysed Diels-Alder reactions with a number of dienes, both cyclic and acyclic, to afford cycloaddition products with very high selectivity.



(i) KO^{t}Bu, THF, 0°C-rt.; (ii) Acryloyl chloride, -78°C, 82%.

Scheme 1

In a series of experiments with (**2**) we studied cycloaddition reactions with cyclopentadiene in the presence of a variety of Lewis acids (Scheme 2, Table 1). In summary, this work established the need for strong dichelating Lewis acids such as the aluminium chlorides of which ethylaluminium dichloride[3] proved to give the best results in terms of both yields and selectivity.



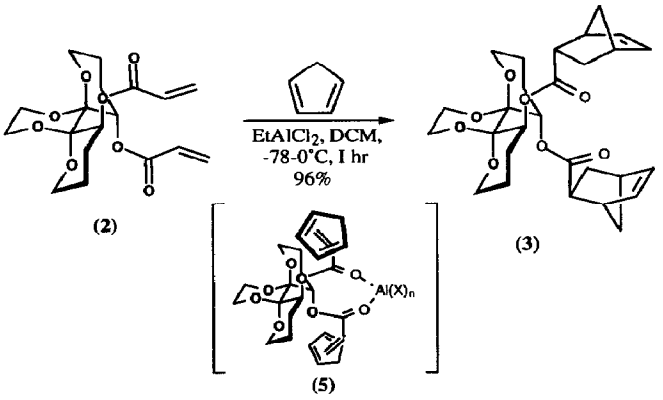
Scheme 2

† *on study leave from the Department of Chemistry, The University of the Orange Free State, P.O. Box 339, Bloemfontein 9300, Rebublic of South Africa.*

Entry	Lewis Acid	Temp. (°C)	Time (hours)	Ratio of (3) : (4) *Endo: Exo* R= (3) : R= (4)	Yield %
1	$EtAlCl_2$	-78	1	23.5:1	99%
2	Et_2AlCl	-78	3	15.5:1	98%
3	$AlCl_3$	-78	23	6.3:1	80%
4	$ZnCl_2$	-78	18	2.6:1	84%
5	$TiCl_4$	0	3.5	2.6:1	40%
6	$SnCl_4$	0	3.5	1.4:1	12%

Table 1

Moreover we found that (**2**) required only one equivalent of Lewis acid to prechelate both acrylate carbonyl groups. The acrylates are oriented in an s-*trans* configured arrangement and the additions proceed to give, as the major product, the symmetrical *bis-endo* adduct (**3**) together with a small amount of a readily separable unsymmetrical *exo-endo, bis*-adduct (**4**). In the best case ($EtAlCl_2$) these diadducts were formed in a combined yield of 99% and the ratio of (**3**) to (**4**) was 23.5:1. The structure of (**3**), which was confirmed by X-ray crystallography, suggests that the reaction proceeds *via* a transition state arrangement as in (**5**) (Scheme 3).



Scheme 3

Using the optimised conditions[4] established for cyclopentadiene, (**2**) was also reacted with other dienes to give the corresponding adducts (**6a-e**)(Scheme 4 and Table 2).

Scheme 4

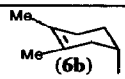
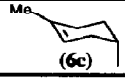
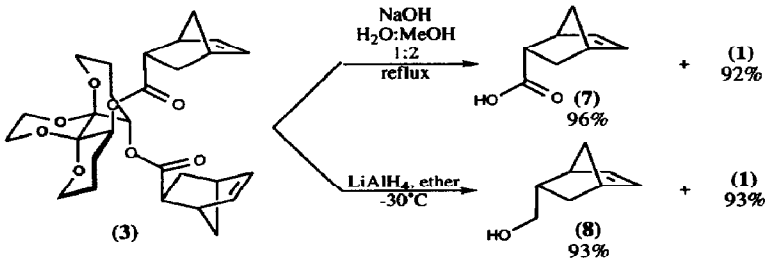
Entry	Diene	Temp. (°C)	Time (hours)	(6) R	Yield
1		-78-0	1	 (3)	96%
2		-78-0	3	 (6a)	89%
3		-78-rt	14	 (6b)	83%
4		-78-0	4	 (6c)	82%
5		-78-rt	16	 (6d)	76%

Table 2

From these data a number of points arise that deserve further comment. In all cases, with the exception of the piperylene reaction (Entry 4), the observed Diels-Alder reactions proceeded to give products of the expected regio- and stereochemical outcome. With piperylene, however, the cycloaddition reaction was relatively slow and, although the expected *ortho*-substitution pattern was observed in the product, a reversal of the normal *endo*-selectivity was observed. In this case the reaction proceeded to give the *exo*-cycloaddition product as the major isomer in an *exo*- to *endo*-ratio of 8.8:1. The symmetrical, all *exo*-product **(6d)** could, however be separated from the unsymmetrical *endo-exo*-product by flash column chromatography.

Cleavage of the Diels-Alder adduct from the auxiliary could be achieved in high yield either hydrolytically (NaOH, MeOH, H_2O, reflux) or reductively ($LiAlH_4$ in diethyl ether, -30°C) (Scheme 5). In neither case was any epimerisation observed and the auxilliary and cleaved adduct could in all cases be separated and recoverd in high yield by extractive methods. Thus in no case was column chromatography required to obtain pure products. For example treatment of **(3)** under hydrolytic conditions gave **(7)** in 96% yield and the recovered auxilliary **(1)** in 92%. Alternatively treatment of **(3)** under reductive conditions gave norbornenol **(8)** and the recovered auxilliary **(1)** both in 93% yield. The cleavage of all Diels-Alder adducts **(6a-d)** proceded smoothly (86-96% yield of cleaved Diels-Alder adduct and >90% recovery of auxilliary) to give the known carboxylic acids which were identical to literature examples.[5]



Scheme 5

The above reactions represent a new opportunity with a C_2-symmetrical dihydroxylated dispiroketal diol (**1**) as a chiral scaffold for asymmetric Diels-Alder reactions with the *bis*-acrylate derivative (**2**) and a variety of simple dienes under Lewis acid-catalysed conditions. The C_2-symmetry and bifunctional format of this auxiliary maximises its effectiveness in being able to react two side chains per asymmetric unit.

Acknowledgement: We thank the S.E.R.C. and the E.P.S.R.C. for funding (to J.V.G. and G.H.C.). Further financial support was provided by Zeneca, the F.R.D., Pretoria (to B.C.B.B.) and the BP endowment (to S.V.L.) at Cambridge.

References and Footnotes

1. Bezuidenhoudt, B.C.B.; Castle, G.H., Ley, S.V.; *Tetrahedron Lett.*, previous paper.
2. (**2**): colourless needles m.p. 141-142 °C (from IPA/hexane); $[\alpha]_D^{26} = -188°$ (c= 0.25, chloroform); μmax (film)/cm^{-1} 2991, 2952, 1721 (C=O), 1635 (C=C), 1406, 1296, 1215, 1094, 1034, 1020, 969, 927, 756, 667; δ_H (200 MHz; $CDCl_3$) 1.40-2.10 (8H, m, 2 × H-3, 2 × H-4, 2 × H-10, 2 × H-11), 3.32-3.68 (4H, m, 2 × H-2, 2 × H-9), 3.60 (2H, m, H_{eq}-14 and H_{eq}-15), 4.10 (2H, m, H_{ax}-14 and H_{ax}-15), 5.58 (2H, dd, J 11.2, 5.0, H-5 and H-12), 5.78 (2H, dd, J 10.02, 1.95, H-2' and H-2"), 6.20 (2H, dd, J 17.3, 10.05, H_{trans}-3' and H_{trans}-3"), 6.48 (2H, dd, J 17.28, 1.96, H_{cis}-3' and H_{cis}-3"); δ_C (50 MHz; $CDCl_3$) 23.5 (C-3 and C-10), 24.5 (C-4 and C-11), 57.9 (C-2 and C-9), 59.1 (C-14 and C-15), 66.5 (C-5 and C-12), 95.4 (C-6 and C-7), 128.4 (C-2' and C-2"), 129.5 (C-3' and C-3"), 165.0 (C-1' and C-1"); *m/z* (EI) 366 $(M)^+$, 306, 297, 243, 225, 126, 99, 71, 55; Found: $(M)^+$, 368.1473. $C_{18}H_{24}O_8$ requires: *M*, 368.1471; Analysis; Found: C, 58.49%; H 6.57%. $C_{18}H_{24}O_8$ requires: C, 58.69%; H, 6.57%.
3. Evans, D.A.; Chapman, K.T.; Bisaha, J.; *J. Am. Chem. Soc.*, **1988**, *110*, 1238.
4. In a standard procedure, to a solution of diacrylate (**2**) (1 mmol) and galvinoxyl (0.1 mmol) in DCM (10 ml) at -78 °C was added dropwise $EtAlCl_2$ (1 M in DCM, 1 mmol). The deep red solution was stirred for 15 minutes and treated with the diene (50 mmol). The reaction was allowed to come to room temperature and stirred for between 1-16 hours. After diluting with DCM (50 ml), 1N HCl (10 ml) was added and the aqueous phase extracted with DCM (2 × 50 ml).The combined organic layers were washed with brine (2 × 30 ml), dried (MgSO4), concentrated *in vacuo* and the products obtained by flash column chromatography.
5. Literature data for hydrolysis products of (**3**), (**6a**) and (**6b**): Kouklovsky, C.; Pouilhès, A.; Langlois, Y.; *J. Am. Chem. Soc.*, **1990**, *112*, 6672; (**6c**) and (**6d**): Nakazaki, N.; Naemura, K.; Kondo, Y.; *J. Org. Chem.*, **1979**, *44*, 16. See also reference 3.

(*Received in UK* 5 *July* 1994; *accepted* 12 *August* 1994)