

0957-4166(94)00194-4

Thermodynamically Controlled Asymmetric Induction: Applications with the Intramolecular Diels-Alder Reaction Involving a Furan Diene

Simon Woo and Brian A. Keay*

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4

Abstract: Treatment of a variety of optically pure IMDAF precursors, containing one asymmetric centre on the sidearm, under thermodynamic conditions with $MeAlCl_2$ (-78°C), provides cycloadducts with up to 5 asymmetric centres of known absolute stereochemistry. The minor cycloadduct can be equilibrated in the presence of $MeAlCl_2$ (-78°C) to provide more of the major isomer. Treatment of the major cycloadduct with excess MeLi provides a decalin ring with up to 6 asymmetric centres, 5 of which are contiguous, in high enantiomeric excess.

In a recent report, Albizati *et al* noted that one of the main advantages of employing thermodynamic control over kinetic control in asymmetric induction is that, in general, a larger number of stereocentres can be established in one step. This ground-state stereocontrol was applied by Albizati's group with success to the asymmetric synthesis of methyl substituted 4,10-diketo-1,7-dioxaspiro[5.5]undecanes.¹ We wish to report on another system which we have been examining that is also amenable to asymmetric transfer under thermo-dynamic control.



In the intramolecular Diels-Alder reaction employing a furan diene (IMDAF) tethered to the dienophile by a four carbon sidearm (Scheme 1), only the adducts with the sidearm oriented *exo* with respect to the oxygen bridge are observed to form.² Therefore, when the sidearm bears a methyl group only two diastereomers 2 and 3 are expected. Cycloadduct 2, with the methyl group on the sidearm in an equatorial position in the newly formed six-membered ring, should be thermodynamically more stable than cycloadduct 3, where the methyl group is in an axial position and suffers a 1,3-diaxial interaction with the bridging oxygen atom. We have previously shown that Lewis acid mediated IMDAF reactions are under thermodynamic



control² and can be diastereoselective when the tether is substituted.³ Therefore, we believed that it would be possible to transfer chirality under thermodynamic control from the stereocentre on the sidearm to generate three (or more) new stereocentres of known absolute stereochemistry via the IMDAF reaction. The stereoselective addition of a nucleophile to the ketone carbonyl and S_N2' ring opening of the resulting oxatricyclo adduct⁴ would then produce an additional stereocentre and provide in high optical purity a richly functionalized molecule with suitable handles for further manipulation. We herein report our findings from studies directed at achieving this goal.

The preparation of the Diels-Alder precursors is illustrated in Scheme 2. (S)-3-(2-Furyl)-2-methyl-1propanol (5) was prepared in high optical purity from Baker's yeast reduction of furan 4.^{5,6} Furan 5 was converted to iodide 7 (via tosylate 6) and hence to allylic alcohols 8a-c.⁷ Oxidation of these alcohols with Fetizon's reagent provided IMDAF precursors 1a-c.^{2,3,8}

Precursor 1a underwent the IMDAF reaction under the oxidation conditions, producing a 4:1 mixture of $2a:3a^9$ in 76% yield, along with a small amount of enone 1a (10%) (Scheme 2). A small amount of 1b also underwent the IMDAF reaction under the oxidation conditions providing a 3:1 mixture of 2b:3b (9%). The bulk of enones 1b and 1c could be made to undergo the IMDAF reaction when treated with 0.1 equivalents of

Enone	Temperature	Time	Ratio of 1:2:3a	Yield of 2+3 ^b
(+)-1b	-78°C	2 h	0:74:26	
		5.5 h	0:100:0	96%
(-)- 1c	-78°C	2 h	10:55:35	
		5.5 h	9:81:10	92%
(-)-1c	-60°C	8 min	34:47:19	
		30 min	6:83:11	ĺ
		2 h	4:92:4	(c)

Table 1: The Results from the IMDAF Reaction of Furans 1b and 1c with 0.1 Equivalents of MeAlCl₂.

a) Ratios determined by integration of ¹H NMR spectra.

b) Isolated yields.

c) NMR study - no yield determined.



MeAlCl₂ at low temperature (Table 1). Enone 1b, when treated with MeAlCl₂ at -78° C for 5.5 hours, formed cycloadduct 2b⁹ exclusively in 96% yield. Under the same conditions, enone 1c produced an 81:10 mixture of 2c⁹:3c in 92% yield along with a small amount of unreacted starting material. In one step, then, the IMDAF reaction produces up to 4 new stereocentres of known absolute and relative stereochemistry.

A number of different observations provided evidence that cycloadducts 2 and 3 are in equilibrium via a retro-Diels-Alder -- Diels-Alder sequence. First, NMR studies¹⁰ at -60°C with enone 1c showed that, over time, the amount of cycloadduct 2c increased at the expense of 3c, changing from a ratio of 47:19 after 8 minutes to 83:11 after 0.5 hours to 92:4 after 2 hours (entry 3, Table 1). Second, for both enones 1b and 1c, a greater proportion of the thermodynamically more stable cycloadducts 2b and 2c was observed with longer reaction times, changing from a ratio of 2b:3b of 74:26 after 2 hours at -78°C to 100:0 after 5.5 hours for 1b, and from 55:35 (2c:3c) after 2 hours to 81:10 after 5.5 hours at -78°C for 1c (entries 1 and 2, Table 1). Finally, and most conclusively, when a pure sample of the thermodynamically less stable cycloadduct 3a was treated with 0.1 equivalents of MeAlCl₂ at -78°C, a 54:46 mixture of 3a:2a was obtained after 5.75 hours (Scheme 3). Treatment of this latter mixture, however, with 1.1 equivalents of MeAlCl₂ provided a 5:95 mixture of cycloadducts 3a:2a after 4 hours (equilibrium is reached faster with larger quantities of Lewis acid). Thus, the minor isomers 3a-c can be recycled to provide higher yields of adducts 2a-c.

As we have previously described,⁴ these oxatricyclo compounds react further with high stereoselectivity when treated with organolithium reagents (Scheme 4). When adduct 2b was treated with methyllithium in diether ether, stereoselective addition to the carbonyl group from the α -face occurred to give axial alcohol 9b.¹¹ This alcohol was analyzed by chiral phase GC (Cydex-B column, 25 m) and determined to have an e.e. of >99%. Alternatively, when 2c was treated with methyllithium in DME, compound 10c,^{11,12} resulting from α -face addition to the carbonyl group and regioselective S_N2' ring-opening from the β -face, was formed. The resulting product contains 6 asymmetric centres, 5 of which are contiguous, of known absolute stereochemistry as well as a double bond and hydroxy groups to allow for further elaboration.



In conclusion, we have established methodology for producing substituted 6,6 fused ring systems with up to 6 asymmetric centres (5 of which are contiguous) in high enantiomeric excess. Chirality is transferred from one stereocentre to 4-6 other centres in only two steps. Synthetic applications of this methodology are currently under investigation.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC), the Merck Frosst Centre for Therapeutic Research (Pointe-Claire, Quebec, Canada), and the University of Calgary for financial support. One of us (SW) thanks NSERC, the Killam Foundation, and the Alberta Heritage Scholarship Fund for postgraduate scholarships.

References and Notes

- 1. Zhao, Y.; Pratt, N.E.; Heeg, M.J.; Albizati, K.F. J. Org. Chem. 1993, 58, 1300.
- Rogers, C.; Keay, B.A. Can. J. Chem. 1992, 70, 2929; Rogers, C.; Keay, B.A. Tetrahedron Lett. 1991, 32, 6477; Rogers, C.; Keay, B.A. Synlett 1991, 353.
- Rogers, C.; Keay, B.A. Can. J. Chem. 1993, 71, 611; Rogers, C.; Keay, B.A. Tetrahedron Lett. 1989, 30, 1349.
- 4. Woo, S.; Keay, B.A. Tetrahedron Lett. 1992, 33, 2661.
- 5. Fuganti, C.; Grasselli, P.; Servi, S.; Högberg, H. J. Chem. Soc., Perkin Trans. I 1988, 3061.
- 6. Since alcohol 5 was very difficult to purify, an optical rotation was not measured. The optical purity of alcohol 5 was determined by comparing the rotation of tosylate 6 to the literature value: $[\alpha]_D^{23} = +6.99$ (c 0.1027, CHCl₃). Lit.⁵ $[\alpha]_D^{20} = +6.97$ (c 1, CHCl₃).
- 7. The optical rotations of compounds **8a-c** were not measured since mixtures of diastereoisomers were formed.
- 8. Enone 1a could not be purified since some cycloadduct 2a would form immediately; therefore, an optical rotation could not be measured. Enone 1b: bp 50-60°C (0.05 torr); $[\alpha]_D^{23} = +8.9$ (c 0.104, CHCl₃). Enone 1c: bp 50-60°C (0.05 torr); $[\alpha]_{435}^{23} = -14.1$ (c 0.106, CHCl₃). (A wavelength of 435 nm was used since a rotation was not observed using the D line of sodium).
- 9. Compound 2a: mp 88.5-90°C; $[\alpha]_D^{23} = +25.9$ (c 0.0418, CHCl₃). Compound 2b: bp 54-58°C (0.05 torr) $[\alpha]_D^{23} = -15.3$ (c 0.0693, CHCl₃). Compound 2c: bp 50-60°C (0.05 torr); $[\alpha]_D^{23} = -33.8$ (c 0.0387, CHCl₃). As very small quantities of the minor cycloadducts 3a-c were isolated, accurate optical rotation determinations were not possible.
- 10. NMR studies were performed on enones 1b and 1c with both catalytic and stoichiometric amounts of MeAlCl₂ to determine optimum conditions for the IMDAF reactions. The amount of Lewis acid did not affect the selectivity noticeably although equilibrium was attained faster with stoichiometric amounts. Some decomposition was noted in some cases at higher temperatures or when 1.1 equivalents of MeAlCl₂ was used, and, for enone 1c, the equilibrium was in favour of starting material with stoichiometric quantities of Lewis acid. Therefore, catalytic quantities of MeAlCl₂ were used at lower temperatures in the IMDAF reaction. This made the workup easier, but longer reaction times were required to obtain the products in reasonable yields.
- 11. Compound **9b**: bp 45-50°C (0.05 torr); $[\alpha]_{D}^{23} = -3.2$ (c 0.0315, CHCl₃). Compound **10c**: mp 139.5-141°C; $[\alpha]_{D}^{22.5} = +40.7$ (c 0.0308, CHCl₃).
- 12. All compounds provided analytical and/or spectroscopic data consistent with their structures.