Tetrahedron Letters, Vol.32, No.27, pp 3147-3150, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

ASYMMETRIC DIELS–ALDER REACTIONS. INVERSE ELECTRON DEMAND REACTIONS OF ESTERS OF 3-HYDROXYPYRAN-2-ONE WITH VINYL ETHERS: USE OF HIGH PRESSURE TO AVOID DECARBOXYLATION OF ADDUCTS

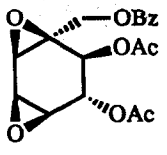
Vichukorn Prapansiri and Edward R. Thornton*

Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104-6323 USA

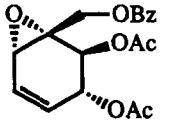
Key Words: Diels–Alder; asymmetric; pyran-2-one; vinyl ether; high-pressure

Abstract: Asymmetric inverse electron-demand Diels–Alder reactions of esters of 3-hydroxypyran-2-one with vinyl ethers proceed under high pressure at ambient temperature, making isolation of the synthetically useful bicyclic adducts feasible. Investigation has revealed that the desired adduct can be synthesized with diastereofacial selectivity, up to 88:12, by reaction of the acetate of 3-hydroxypyran-2-one with chiral 8-(3,5-dimethylphenyl)menthyl vinyl ether.

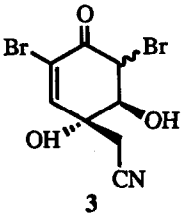
Several α-hydroxycyclohexenecarboxylic acid derivatives in which the ring α-carbon atom is stereogenic are useful as intermediates in organic synthesis.[1] The carboxylic acid and ene groups might be transformed to give target molecules having important and diverse pharmacological properties, including inhibition of Lewis lung carcinoma (cyclohexene oxides: crotepoxide (**1**), senepoxide (**2**)[2]) and antimicrobial activity (**3**)[3].



1

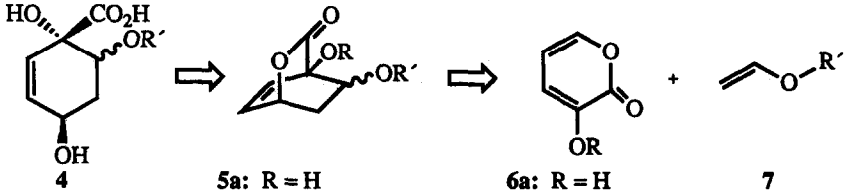


2



3

As part of our ongoing research program on asymmetric Diels–Alder reactions, we envisioned that hydroxy acid **4**, which is intriguing as a potential intermediate in compact syntheses of such naturally occurring cyclohexene derivatives, could be obtained via ring opening of bicyclic compounds of type **5**. Bicyclic adducts **5** could be directly obtained from [4+2] cycloaddition of 3-hydroxypyran-2-ones **6** with vinyl ethers **7**, as shown in the Scheme below.



4 **5a:** R = H **6a:** R = H **7**

5b: R = $COCH_3$ **6b:** R = $COCH_3$

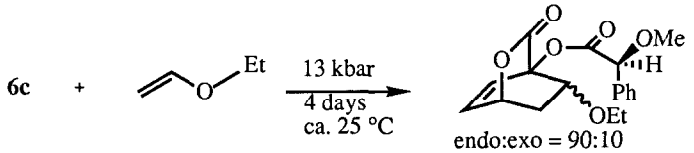
5c: R = CO(OMe, H, Ph) **6c:** R = CO(OMe, H, Ph)

In this letter we wish to report *the first study towards asymmetric synthesis of the bicyclic compound 5a via inverse-electron demand Diels–Alder reactions of pyrones 6 and vinyl ethers 7, including the application of*

high pressure-methodology to prevent extrusion of carbon dioxide from the bicyclic adducts. Diels–Alder reactions of the parent, **6a**, with electron-poor dienophiles have previously been reported (thermal[4] and high-pressure[5]), and 3-arylsulfonyl and 3-arylsulfoxide analogs have been shown to give corresponding adducts.[6] It has been shown that both reaction rate[7] and facial selectivity[8] can be enhanced at high pressure.

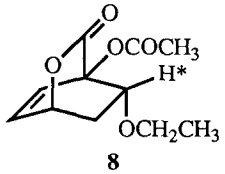
A priori, the asymmetric synthesis might be achieved by use of either a chiral diene or a chiral dienophile. We have therefore examined both of these strategies in order to elucidate the requirements for high selectivity.

Chiral Diene. Since 1-(*O*-methylmandeloxy)butadiene has been shown to give high diastereofacial selectivity in asymmetric Diels–Alder reaction with acrolein,[9,10] we employed the same chiral controller group in the cycloaddition of diene **6c** with a simple vinyl ether, **7** (R′ = Et). Pyrone **6c** was synthesized by esterification of the parent **6a**[11] with *O*-methylmandelic acid with DCC/DMAP in CH_2Cl_2, slightly modifying a previous procedure used with alcohols.[12] Cycloaddition proceeded smoothly at 13 kbar/4 days, giving the bicyclic adduct in 94% yield as an endo/exo mixture (eq 1).

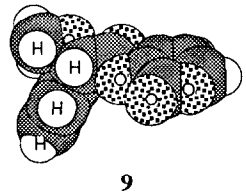


endo:exo = 90:10
diastereomeric ratio = 55:45 (1)

The structures of exo and endo isomers are assigned based on comparison with the ^1H NMR spectra of model compound **8** and its exo isomer. We have shown **8** to be endo by ^{13}C-{^1H} NOE-difference spectra: irradiation of H* gave 11.6% NOE at the bridge C=O; the latter C=O was identified by irradiation of the acetyl Me protons, giving an NOE at the other (acetyl) C=O. Although we considered it plausible that **6c** would have a



8



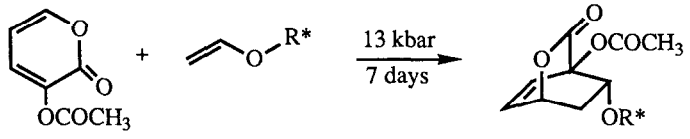
9

significant conformational preference which could be translated into significant diastereofacial selectivity, the selectivity obtained was low (55:45). As seen in **9**, a possible preferred conformation might place the two C=O groups anti both for steric reasons and to avoid dipole–dipole[13] repulsions, the *O*-methylmandelate group in the approximately perpendicular conformation we have previously observed in X-ray structures.[10] Appropriate molecular mechanics parameters are not available, but it is possible that the predicted conformational preference does exist, yet the ester group is forced to be slightly noncoplanar with respect to the pyrone ring, such that the phenyl group is tipped just out of the path of any approaching dienophile, making both faces of the diene nearly equally accessible.

The hydroxyl of pyrone **6a** must be protected. Reaction of **6a** with isomenthyl vinyl ether for at 13 kbar/7 days, ca. 25 °C, led to isomenthol in 100% isolated yield, presumably via decarboxylative aromatization of **5a**.

Chiral Dienophiles. The alternative strategy, involving a protected achiral pyrone, 2-acetoxypyran-2-one, **6b**, and a chiral vinyl ether gave much higher facial selectivities. Pyrone **6b** was synthesized by acetylation of **6a** with acetyl chloride/pyridine. Chiral vinyl ethers were prepared by mercuric acetate-catalyzed exchange reaction between the parent alcohol and *n*-butyl vinyl ether or isobutyl vinyl ether.[14] Cycloaddition required 7 days at ca. 25 °C to reach a satisfactory, though not optimal, yield of **5b**. Diastereofacial selectivities ranged from 52:48 to 88:12 (Table I).

Table I. Cycloaddition Reactions Between Pyrone **6b** and Chiral Vinyl Ethers Under High Pressure[a]



6b **5b**

Entry	R*	Yield, %[b,c]	Diastereomeric ratio[d]
1	Ph(CH_3)CH-	76	60:40
2	Ph(*t*-Bu)CH-	84	73:27
3	α-Naphthyl(*t*-Bu)CH-	56	69:31
4	Ph(cyclohexyl)CH-	67	53:47
5	Ph(CO_2CH_3)CH-	84[e]	74:26
6	Bornyl	74	58:42
7	Fenchyl	75	68:32
8	Menthyl	80	53:47
9	Isomenthyl	74	52:48
10	2-Phenylcyclohexyl	64	65:35
11	2-(α-Naphthyl)cyclohexyl	66	79:21
12	8-Phenylmenthyl	60	81:19
13	8-(β-Naphthyl)menthyl	75	87:13
14	8-(3,5-Dimethylphenyl)menthyl	75	88:12

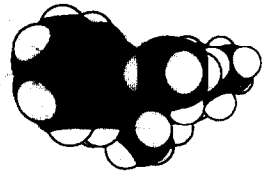
[a]Reactions were run in teflon tubes on a 0.5 mmol scale, with 1.2 to 2 equiv of vinyl ethers in 1 M solution in CH_2Cl_2. [b]Isolated yields. [c]All new compounds gave characteristic ^1H NMR and HRMS spectra. [d]Ratios determined by 250 MHz ^1H NMR integration of the *COCH3* and/or bridgehead *H* signals in crude reaction mixtures. [e]Yield determined by ^1H NMR.

Structures of adducts **5b** were confirmed by their ^1H NMR spectra, which show olefinic protons at ca. 6.2–6.5 ppm and the ^{13}C signal of the ester bridge carbonyl at 167–170 ppm. The cycloadditions gave exclusively endo adducts, assigned based on model compound **8**.

Three basic structural features of chiral vinyl ethers were explored in this study, i. e., simple acyclic chiral vinyl ethers (entries 1–5), chiral vinyl ethers derived from camphor-related derivatives (entries 6, 7), and cyclohexane derivatives (entries 8–14). From a mechanistic point of view, asymmetric induction arising from acyclic chiral vinyl ethers has not yet been well clarified. However, it has been predicted from ab initio molecular orbital calculation that the lowest energy conformation of α-methylbenzyl vinyl ether[15] (entry 1) has the methyl group oriented away from the enol moiety so that the phenyl ring is nearly orthogonal to the enol. A high selectivity, ascribed to an *extended conformation* of a chiral vinyl ether was found using a bulky Lewis acid catalyst in its Diels–Alder reaction with a pyrone sulfone.[6c] Facial selectivity should originate from the preferred approach of the diene to the enol face opposite from the phenyl group. The facial selectivity would then be controlled by the difference in size between the phenyl and the methyl groups. Conceptually, if this preference be sufficient, the facial selectivity might be improved by increasing the size of either the alkyl chain or the phenyl group. Experimentally, replacement of the methyl group with a *tert*-butyl group did indeed increase the diastereofacial selectivity from 60:40 (entry 1) to 73:27 (entry 2). Enlargement of the phenyl ring size to the napthyl (entry 3) had almost no effect, in fact, we found a slight decrease in selectivity.

To increase the facial bias further, cyclic controller groups were employed. The camphor-related groups (entries 6, 7) did not provide strong control, but substituted cyclohexanes provided major improvements. Use of 8-phenylmenthol had given strong stereocontrol in certain other reaction types.[16,17] The selectivity of 81:19 (i. e., 4.3:1) obtained from 8-phenylmenthyl vinyl ether (entry 12) was very promising compared with simpler

systems (entries 8–10). Analogues of this lead compound gave even higher ratios, 87:13 for 8-(β-naphthyl)-menthyl vinyl ether (entry 13) and 88:12 (7.3:1) for 8-(3,5-dimethylphenyl)menthyl vinyl ether (entry 14). These results can be explained on steric grounds: the *Re* face of the enol is shielded by the aromatic group and the *Si* face reacts preferentially.[18] This is seen in the MM2-minimized enol ether structure shown, where the 8-(β-naphthyl)menthyl enol C=C is horizontal, in the center of the structure, and is viewed approximately from its H_2C end—the lower C=C face is considerably more hindered than the upper. The high selectivity can be nicely explained by approximate retention of this conformational preference in the transition structures for diene attack on the two faces of the C=C.



In this work we have (1) demonstrated that 3-acyloxypyran-2-ones can indeed behave as electron-accepting dienes in inverse-electron demand Diels–Alder reactions. In spite of the attached oxygen atoms which make these dienes so electron-rich that they failed to react under thermal or Lewis-acid catalysed conditions, under high pressure the reaction proceeded smoothly to give the bicyclic adducts **5**. (2) We have examined both chiral diene and chiral dienophile strategies and have thus shown that chiral enol ethers are capable of good levels of asymmetric induction. (3) Asymmetric synthesis of bicyclic **5** was achieved at a satisfactory level (nearly 90:10). Isolation of the major diastereomer would give **5** in optically pure form. Its uses in organic synthesis are of considerable interest.

Acknowledgment. We thank Mr. John Dykins, Chemistry Mass Spectrometry Facility, and Dr. George Furst, Chemistry NMR Facility, for their splendid assistance. Support by the National Institutes of Health is gratefully acknowledged.

References and Notes

1. For recent use of quinic acid in organic synthesis, see: (a) White, J. D.; Cammack, J. H.; Sakuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 8970–8972. (b) Shing, T. K. M.; Tang, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 312.
2. For a review of cyclohene oxides, see: Thebtaranonth, C.; Thebtaranonth, Y. *Acc. Chem. Res.* **1986**, *19*, 84–90.
3. Capon, R. J.; MacLeod, J. K. *Aust. J. Chem.* **1987**, *40*, 341–346.
4. Corey, E. J.; Kozikowski, A. P. *Tetrahedron Lett.* **1975**, *16*, 2389–2392.
5. Gladysz, J. A.; Lee, S. J.; Tomasello, J. A. V.; Yu, Y. S. *J. Org. Chem.* **1977**, *42*, 4170–4172.
6. (a) Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667–670. (b) Posner, G. H.; Haces, A.; Harrison, W.; Kinter, C. M. *J. Org. Chem.* **1987**, *52*, 4836–4841. (c) Posner, G. H.; Kinter, C. M. *J. Org. Chem.* **1990**, *55*, 3967–3969. (d) Posner, G. H.; Nelson, T. D. *Tetrahedron* **1990**, *46*, 4573–4586.
7. Dauben, W. G.; Gerdes, J. M.; Look, G. C. *Synthesis* **1986**, 532–535. For excellent reviews, see: (a) Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999–1027. (b) Jurczak, J. In *Organic High Pressure Chemistry;* le Noble, W. J. , Ed.; Elsevier: Amsterdam, **1988**, pp 304–356.
8. Tietze, L. F.; Hübsch, T.; Voss, E.; Buback, M.; Tost, W. *J. Am. Chem. Soc.* **1988**, *110*, 4065–4066.
9. Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595–7596.
10. Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1988**, *29*, 5225–5228.
11. Wiley, R. H.; Jarboe, C. H. *J. Am. Chem. Soc.* **1956**, *78*, 2398–2401.
12. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374.
13. Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297–304.
14. Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828–2833.
15. Charlton, J. L.; Plourde, G. L.; Penner, G. H. *Can. J. Chem.* **1989**, *67*, 1010–1014.
16. Oppolzer, W.; Robbiani, C.; Bättig, K. *Helv. Cheim. Acta* **1980**, *63*, 2015–2018.
17. Whitesell, J. K. *Acc. Chem. Res.* **1985**, *18*, 280–284.
18. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908–6909.

(Received in USA 12 March 1991)