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CATALYTIC ENANTIOSELECTIVE DIELS-ALDER ADDITION TO FURAN PROVIDES A DIRECT SYNTHETIC ROUTE TO MANY CHIRAL NATURAL PRODUCTS

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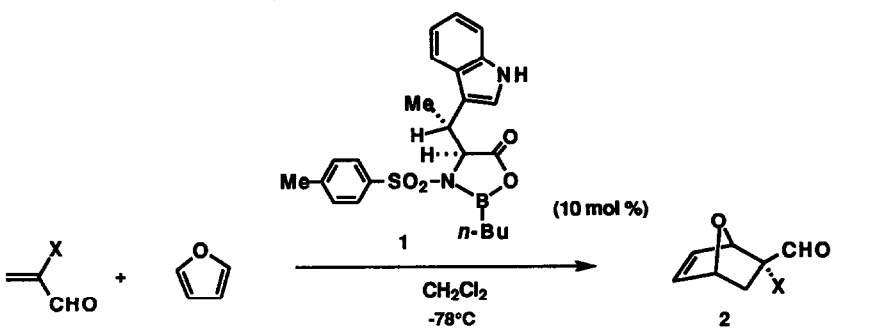
Summary: *An oxazaborolidine derived from N-tosyl ($\alpha S,\beta R$)-β-methyltryptophan (**1**)catalyzes the Diels-Alder reaction of 2-bromoacrolein and furan with 96 : 4 enantioselectivity, leading to an efficient synthesis of numerous chiral 7-oxabicyclo[2.2.1]heptene derivatives.*

The utility of 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives as key intermediates for the synthesis of important types of natural products has recently been demonstrated convincingly.[1,2] A large number of selective transformations of the 7-oxabicyclo[2.2.1]heptene system[1] endow this nucleus with impressive versatility.[1] One obstacle to the realization of the full potential of this ring system in synthesis has been the need for expensive chiral controller groups and arduous separations of diastereomeric mixtures in order to obtain enantiomerically pure compounds. In this paper we report the successful application of the oxazaborolidine **1**, derived from *N*-tosyl ($\alpha S,\beta R$)-β-methyltryptophan,[3,4] as a catalyst for the enantioselective synthesis of 7-oxabicyclo[2.2.1]heptene derivatives by Diels-Alder addition to furan. It has been shown previously that 5 mole % of **1** catalyzes the reaction between cyclopentadiene and 2-bromo- or 2-chloroacrolein to afford the 2-(*R*), 2-*exo*-formyl Diels-Alder adduct with at least 200 : 1 enantioselectivity.[3,4]

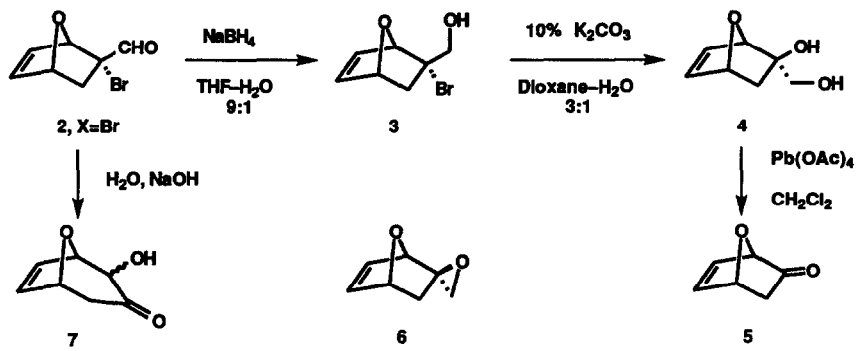
The reaction of 5 equiv of furan with 2-bromoacrolein in the presence of 10 mole % of catalyst **1**[4] in dichloromethane at -78 °C was complete in 5 h and gave the Diels-Alder adduct **2**, X=Br, in >98% yield and



X=Br, 92% ee (*exo*/*endo*=99/1)
X=Cl, 90% ee (*exo*/*endo*=99/1)

96 : 4 enantioselectivity, as determined by 500 MHz ^{1}H NMR analysis of the α-methoxy-α-(trifluoromethyl) phenylacetic (MTPA) ester of the corresponding primary alcohol (**3**, from $NaBH_4$ reduction of **2**).[5,6] The adduct **2**, X=Cl, was also obtained in >98% yield under these conditions with 95 : 5 enantioselectivity. The *N*-tosyl carboxylic acid precursor of **1** was efficiently recovered for reuse in each case. Interestingly, the analog of catalyst **1** lacking the β-methyl group (derived from *N*-tosyl-(*S*)-tryptophan) was not as effective in catalyzing the formation of Diels-Alder product **2** and considerably lower reaction rate and yield were noted.

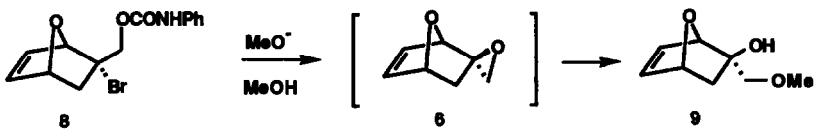
The Diels-Alder adduct **2**, X=Br, was converted to 7-oxabicyclo[2.2.1]hept-5-en-2-one (**5**) in a simple way commencing with reduction by $NaBH_4$ in 9 : 1 THF–H_2O to form bromohydrin **3** (>98% yield). A single recrystallization of **3** from ether–hexane at -20 °C gave crystalline **3**, mp 67 °C, of >99% enantiomeric purity as determined by 500 MHz analysis of the MTPA ester. When bromohydrin **3** was heated at reflux with a 10% solution of K_2CO_3 in 3 : 1 dioxane–water for 16 h it was transformed into the oily diol **4** (92%). Under these conditions epoxide **6** (prepared from **3** and KOtBu in THF at 0 °C) is also cleaved to diol **4**, clearly by S_N2 attack of HO^- on the oxirane methylene group. Treatment of diol **4** with $Pb(OAc)_4$ in CH_2Cl_2 at 0 °C produced ketone **5**, $[\alpha]_D^{23}$ + 856° (c=0.25, CH_2Cl_2),[7] silica gel tlc R*f* (1 : 1 hexane–EtOAc) 0.69, in 85% yield.[8]



Ketone **5**, a valuable intermediate for the synthesis of many natural products,[1,2] can be prepared in pure form from the Diels-Alder adduct **2**, X=Br, (from the dienophile 2-bromoacrolein) in 78% overall yield in enantiomerically pure form without chromatography. Because of the ready availability by the catalytic Diels-Alder route of **5** or its enantiomer, many interesting syntheses take on a more practical character.

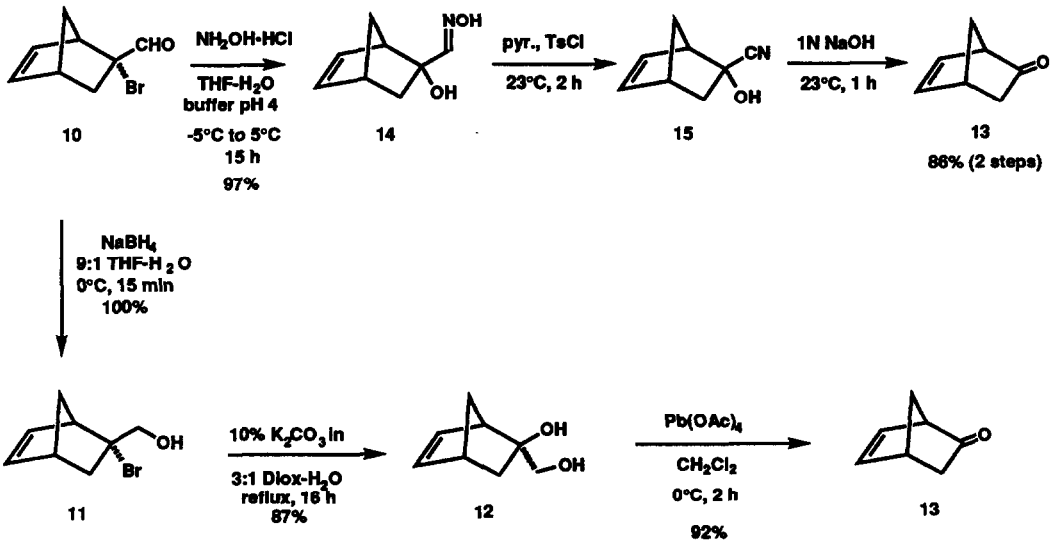
Attempts to convert **2**, X=Br, via the oxime to ketone **5**, using methodology which has been described earlier[3] in the bicyclo[2.2.1]heptane series were unsuccessful. Although the oxime of **2**, X=Br, could be prepared, it could not be converted to the corresponding α-hydroxy oxime (cf. ref 3) or α-bromo nitrile under a wide variety of conditions. Treatment of **2**, X=Br, with 1*M* aq NaOH resulted in transformation to the

diastereomeric ring-expanded α-hydroxy ketones **7** in 88% yield. Bromohydrin **3** could be converted to the urethane derivative **8** by reaction with phenylisocyanate and triethylamine in CH_2Cl_2 at 23 °C for 1 h. Exposure of **8** to potassium carbonate in methanol at reflux for 6 h produced the methyl ether **9** (82%) as a colorless oil. The pathway of this interesting reaction appears to be by the sequence: (1) methanolysis to bromohydrin **3**, (2) ring closure to epoxide **6**, and (3) S_N2 displacement by methoxide to form **9**. A control experiment demonstrated that epoxide **6** was indeed transformed into methyl ether **9** by methanolic potassium carbonate at reflux for 6 h.



8 **6** **9**

The ease of oxirane ring cleavage with hydroxide or methoxide nucleophiles in protic media is not specific to the 7-oxabicyclo[2.2.1]heptene series. The (2*R*)-bromo aldehyde **10** from the catalytic enantioselective addition of cyclopentadiene to 2-bromo acrolein[3,4] can also be transformed via the bromohydrin **11** and diol **12** to bicyclo[2.2.1]hept-5-en-2-one (**13**) as illustrated below. The overall yield of **13** by this process (80%) compares favorably with that for the conversion of **2**, X=Br, to **5** and also to that for the transformation of adduct **10** to **13** via the α-hydroxy oxime **14** and cyanohydrin **15** by an optimized version of the sequence described earlier.[3,9]



10 **14** **15** **13** 86% (2 steps)

11 **12** **13**

We have also investigated the extension of this catalytic enantioselective methodology involving 2-bromo- and 2-chloroacrolein to various pyrrole derivatives, but so far have obtained only negative results. Diels-Alder products were not observed using *N*-mesyl, *N*-tosyl-, *N*-triflyl-, *N*-benzyloxycarbonyl-, or *N*-t-butoxycarbonylpyrrole under a variety of conditions.[10]

References and Notes:

1. For a review, see Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173.
2. For some key applications of 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives, see (a) Eggette, T. A.; de Koning, H.; Huisman, H. O. *J. Chem. Soc., Perkins Trans. I* **1978**, 980 (prostaglandins). (b) Just, G.; Lim, M. I. *Can. J. Chem.* **1977**, *55*, 427, 2993; Just, G.; Kim, S. *Tetrahedron Lett.* **1976**, 1063 (nucleosides). (c) Nelson, W. L.; Allen, D. R.; Vincenzi, F. F. *J. Med. Chem.* **1971**, *14*, 698 and Kotsuki, H.; Nishizawa, H. *Heterocycles* **1981**, *16*, 1287 (muscarinics). (d) Suami, T.; Ogawa, S.; Nakamoto, K.; Kasahara, I. *Carbohydr. Res.* **1977**, *58*, 240; Ogawa, S.; Kasahara, I.; Suami, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 118 and Reynard, E.; Reymond, J.-L.; Vogel, P. *Synlett* **1991**, 469 (antibiotics). (e) Murai, A.; Takahashi, K.; Taketsuru, H.; Masamune, T. *J. Chem. Soc. Chem. Comm.* **1981**, 221 (avenaciolides). (f) Ogawa, S.; Iwasawa, Y.; Nose, T.; Suami, T.; Ohba, S.; Ito, M.; Saito, Y. *J. Chem. Soc. Perkin Trans I* **1985**, 903 (cyclitols).
3. Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966.
4. Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290.
5. Catalyst **1** was prepared in the following way. *N*-Tosyl ($\alpha S,\beta R$)-β-methyltryptophan[4] (2.06 g, 5.6 mmol) and *n*-butylboronic acid (0.60 g, 6.7 mmole) in a 100-ml rb. flask equipped with magnetic stirrer, Soxhlet extractor with reflux condenser having a rubber stopple at the top was connected to a vacuum manifold and placed under nitrogen. A thimble in the extractor contained layers of sand (3 cm, bottom) and CaH_2 (3 cm, top). After the addition of 20 ml of dry THF and 40 ml of dry toluene, the mixture was heated at rapid reflux for 20 h using an oil bath heated to >165 °C. The reaction flask was quickly disconnected and attached to a vacuum line, and the solvent was removed *in vacuo* leaving catalyst **1** as a colorless viscous oil which was stored in a tightly sealed flask as a 0.1*M* solution in 9 : 1 toluene–THF. The solvent was removed *in vacuo* and exchanged with CH_2Cl_2, toluene or other solvent just prior to the Diels-Alder reaction. THF serves to stabilize toluene solutions of catalyst **1**. The following data were obtained for pure **1**. ^1H NMR ($CDCl_3$): δ 0.6 (3H, t, J=4.1Hz), 0.7 - 1.4 (6H, m), 1.675 (3H, d, J=7.4Hz), 2.43 (3H, s), 4.17 (1H, d, J=3.06), 4.25 (1H, qd, J=7.4, 3.06Hz), 7.01 (1H, d, J=2.5Hz), 7.1 - 7.2 (2H, m), 7.35 (3H, m), 7.73 (2H, d, J=8.3Hz), 7.81 (1H, d, J=7.86), 8.28 (1H, br s). ^{13}C NMR (CD_2Cl_2): δ 13.8, 17.3, 21.7, 25.1, 25.3, 34.5, 66.8, 111.4, 114, 120, 120.6, 122.5, 123.1. ^{11}B NMR: δ (BF_3•Et_2O) 35. IR (CH_2Cl_2): 1729 cm^{-1}.
6. Spectral data for **2**, X=Br,: ^1H NMR ($CDCl_3$): δ 1.60 (1H, d, J=13Hz), 2.80 (1H, m), 5.1 - 5.25 (2H, m), 6.45 (1H, m), 6.6 (1H, m), 9.45 (1H, s, exo). ^{13}C NMR ($CDCl_3$): δ 25.68, 36.19, 62.93, 79.76, 80.782, 133.510, 138.609, 190.547. IR (thin film): 2960, 1729, 1017 cm^{-1}.
7. Warm, A.; Vogel, P. *Helv. Chim. Acta* **1987**, *70*, 690 report $[\alpha]_D^{23}$ + 860° for ketone **5**.
8. Spectral data for **5**: ^1H NMR (neat): δ 6.75 (dd, J=1.6Hz, 5.8Hz, 1H), 6.48 (dd, J=1.8Hz, 5.8Hz, 1H), 5.32 (d, J=4.2Hz, 1H), 4.54 (br s, 1H), 2.25 (dd, J=15.8, 4.2Hz, 1H), 1.90 (d, J=15.8Hz, 1H). ^{13}C NMR ($CDCl_3$): 207.72, 142.372, 130.74, 82.27, 79.14, 34.18. IR (neat): 3030, 1775, 1618 cm^{-1}.
9. We are indebted to Dr. Edmund Ellsworth for the details of the optimized procedures for the transformation of **10** to **13** via **14** and **15**.
10. This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation.

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