Tetrahedron Letters, Vol. 33, No. 46, pp. 6935-6938, 1992
Printed in Great Britain

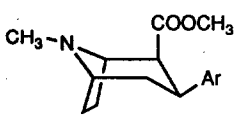
0040-4039/92 $5.00 + .00
Pergamon Press Ltd

ENANTIOSELECTIVE SYNTHESIS OF TROPANES BY REACTION OF RHODIUM-STABILIZED VINYLCARBENOIDS WITH PYRROLES

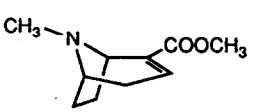
Huw M. L. Davies* and Nicholas J. S. Huby
Department of Chemistry, Wake Forest University, Box 7486,
Winston-Salem, North Carolina 27109

Summary: Rhodium(II) catalyzed decomposition of vinyldiazomethanes containing either (R)-pantolactone or (S)-lactate as chiral auxiliary in the presence of N-(tert-butoxycarbonyl)pyrrole resulted in an enantioselective entry to tropanes by a tandem cyclopropanation/Cope rearrangement.

For close to a century, the tropane alkaloids have occupied a prominent position as targets for organic synthesis.[1] In recent years a resurgence of interest in these compounds has occurred, particularly with the recognition that 3-aryl-8-azabicyclo[3.2.1]octane-2-carboxylates (**1**) are valuable probes to study the neurochemistry of cocaine abuse.[2] Currently, the most practical synthesis of **1** is through the 1,4-addition of Grignard reagents to anhydroecgonine methyl ester (**2**) which is derived from cocaine.[2,3] As more varied structural derivatives of **1** are required, an alternative synthesis which does not begin with cocaine would be highly desirable. We have recently reported that a new approach for the synthesis of tropane alkaloids is possible through the reaction of rhodium-stabilized vinylcarbenoids with pyrroles.[4] In this communication we describe the extension of this process into an asymmetric mode leading to a short synthesis of enantiomerically enriched (-)-**2**.



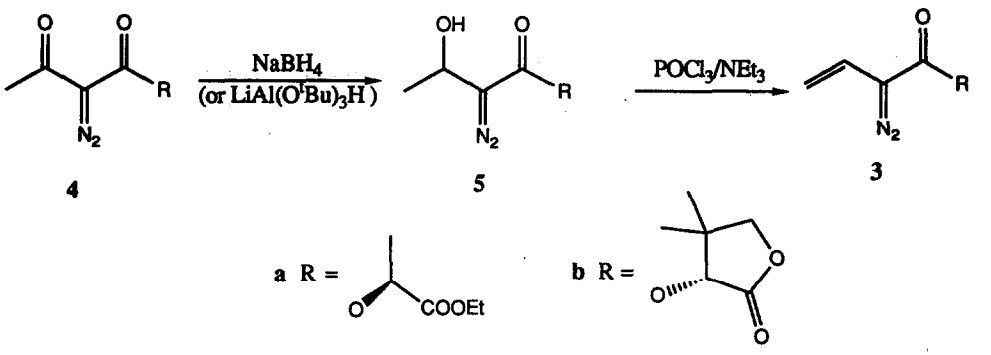
1



2

Asymmetric cyclopropanation with vinyldiazomethanes containing either (R)-pantolactone or (S)-lactate as chiral auxiliary offers a practical alternative[5] to the usual approach of asymmetric cyclopropanation employing chiral catalysts.[6] In order to apply this strategy to the synthesis of **2**, the vinyldiazomethanes **3a**[7] and **3b** were required. The diazoacetoacetates **4** were prepared by reaction of the appropriate alcohol with diketene followed by a diazo transfer reaction with *p*-acetamidobenzenesulfonyl azide. Reduction of **4** to the alcohols **5** was readily achieved with either sodium borohydride (for **4a**[7]) or lithium (*tert*-butoxy)aluminum hydride (for **4b**). The alcohols **4** were dehydrated[8] to form the vinyldiazomethanes **3a**[7] (58% yield) and **3b** (23% yield).

Scheme 1



A fairly narrow window of reaction conditions exists for the successful formation of tropanes from the reaction of rhodium(II)-stabilized vinylcarbenoids with pyrroles.[4] The vinyldiazomethanes with single electron withdrawing groups are prone to rearrangement to pyrazoles and must be used immediately. Non-polar solvents are required or the vinylcarbenoid will display electrophilic character at the vinyl terminus. Moderately vigorous reaction conditions (refluxing hexane or toluene) were originally required to ensure rapid Cope rearrangement of the pyrrolinocyclopropane intermediate and thus avoid *bis* cyclopropanation of the pyrrole. As low temperatures would be expected to enhance the extent of stereoselection, modified conditions were developed whereby a chilled (0 °C) solution of **3** in pentane was added dropwise over 4 h to a stirred solution of the rhodium(II) carboxylate (0.01 equiv) and N-(*tert*-butoxycarbonyl)pyrrole (5 equiv) in pentane, heated under reflux. After removal of excess pyrrole by flash chromatography, the diastereoselectivity was determined by NMR analysis of the crude reaction mixtures at 95 °C.[9] Based on our results on cyclopropanation of styrene,[5] rhodium(II) octanoate was chosen as catalyst and this led to the tropane system **6a** in 66% de with the (S)-ethyl lactate derivative **3a**. The (R)-pantolactone derivative **3b** resulted in similar levels of asymmetric induction on formation of **6b** (69% de). Significantly lower levels of diastereoselectivity was observed when the bulkier rhodium(II) pivalate catalyst was used (Table 1).

Scheme 2

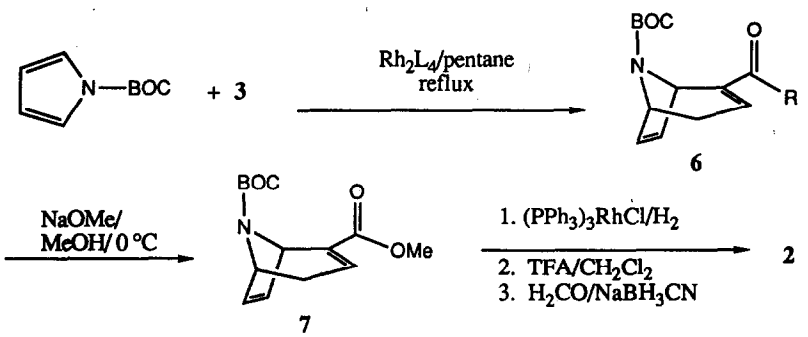


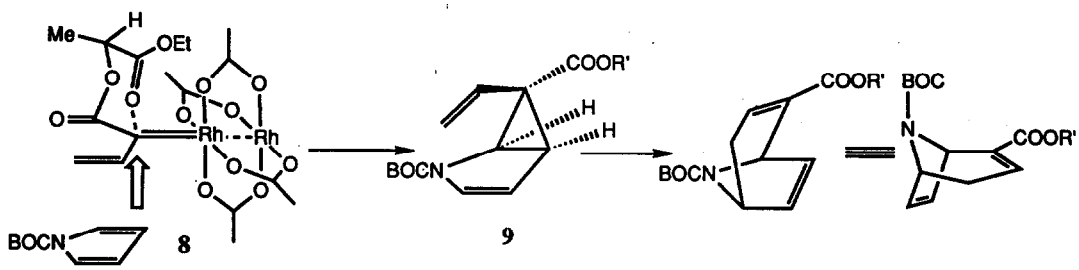
Table 1: Formation of **6** by rhodium(II) catalyzed decomposition of **3**

Substrate	Catalyst	Solvent	Product	Yield,%	de,% (mjr diast)
3a	$Rh_2(OOct)_4$	pentane	**6a**	82	66 (1R)
3a	$Rh_2(OPiv)_4$	pentane	**6a**	94	46 (1R)
3b	$Rh_2(OOct)_4$	pentane	**6b**	64	69 (1S)
3b	$Rh_2(OPiv)_4$	pentane	**6b**	52	10 (1S)

Determination of the absolute stereochemistry of the tandem cyclopropanation/Cope rearrangement was achieved through conversion of the initial product **6a** to anhydroecgonine methyl ester **2**. The chiral auxiliary in **6a** was removed through methanolysis to give the methyl ester **7** (92% yield, $[\alpha]_D^{25}$ = +35.3 ° ($CHCl_3$, c 2.28). Catalytic hydrogenation of **7** with Wilkinson's catalyst, followed by deprotection with TFA and reductive methylation with sodium cyanoborohydride generated enantiomerically enriched (-)-anhydroecgonine methyl ester (47% yield from **7**, ~60% ee, $[\alpha]_D^{25}$ = -25.7 °(MeOH, c 1.48), lit value[10] = -43 ° (MeOH, c 1.5)). The (R)-pantolactone auxiliary was shown to have resulted in the opposite asymmetric induction to (S)-lactate by methanolysis of **6b** to predominantly ent-**7** (83% yield, $[\alpha]_D^{25}$ = -36.6 ° ($CHCl_3$, c 0.295)) as this product displayed the opposite optical rotation to the product derived from **6a**.

The asymmetric induction parallels the results that we have previously obtained in the cyclopropanation of styrene and may be rationalized as illustrated in Scheme 3.[5] The critical element of this model is that the carbonyl of the chiral auxiliary is considered to interact with one face of the carbenoid which directs attachment of the pyrrole to the opposite face. The preferred orientation of the (S)-ethyl lactate auxiliary is as shown in **8**, whereby the methyl group at the stereogenic center is pointing away from the bulk of the catalyst. A similar interaction between a carbenoid and ester funtionality has been proposed by Doyle[6j] to explain the enantioselectivity observed with the $Rh_2(MEPY)_4$ catalyst. The induced stereochemistry in the cyclopropanation step is then transformed to the final product by means of a Cope rearrangement of the divinyl cyclopropane **9**.

Scheme 3



In summary, the rhodium(II) catalyzed decomposition of vinyldiazomethanes **3** in the presence of N-(*tert*-butoxycarbonyl)pyrrole leads to the enantioselective synthesis of (-)-anhydroecgonine methyl ester (**2**). In principle, this chemistry could be extended to more highly functionalized vinyldiazomethanes and pyrroles and thus the potential exists for the enantioselective synthesis of a range of tropane derivatives.

Acknowledgement: Financial support of this work by the National Institute on Drug Abuse (DA 06301) is gratefully acknowledged.

References and Notes.

1. (a) Lounasmaa, M. *Alkaloids* **1988**, *33*, 1. (b) Fodor, G.; Dharanipragada, R. *Nat. Prod. Reports* **1990**, *7*, 540. (c) Fodor, G. *Alkaloids* **1960**, *6*, 145. (d) Holmes, H. L. *Alkaloids* **1950**, *1*, 271.
2. (a) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969. (a) Lewin, A. H.; Gao, Y.; Abraham, P.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. *J. Med. Chem.* **1992**, *35*, 135. (c) Abraham, P.; Pitner, J. B.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. *J. Med. Chem.* **1992**, *35*, 141.
3. Clarke, R. L.; Daum, S. J.; Gambino, A. J.; Aceto, M. D.; Pearl, J.; Levitt, M.; Cumiskey, W. R.; Bogado, E. F. *J. Med. Chem.* **1973**, *16*, 1260.
4. Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696.
5. Davies, H. M. L.; Cantrell, W. R., Jr. *Tetrahedron Lett.* **1991**, *32*, 6509.
6. (a) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, 5239. (b) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1982**, *23*, 685. (c) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta*, **1988**, *71*, 1553. (d) Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron*, **1992**, *48*, 2143. (e) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (f) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (g) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T. *Tetrahedron Lett.* **1990**, *31*, 6613. (h) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Muller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423. (i) Protopopova, M. N.; Doyle, M. P.; Muller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, *114*, 2755. (j) Doyle, M. P. *Recl. Trav. Chim. Pays-Bas.* **1991**, *110*, 305. (k) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *Chem. Commun.* **1990**, 361. (l) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 5173.
7. Davies, H. M. L.; Hoougland, P. W.; Cantrell, W. R., Jr. *Synth. Commun.* **1992**, *22*, 971.
8. Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144.
9. High temperatures were required to avoid broadening of NMR signals because of hindered rotation around the amide bond.
10. Campbell, H. F.; Edwards, O. E.; Kolt, R. *Can J. Chem.* **1977**, *55*, 1372.

(Received in USA 28 July 1992)