Pergamon

Tetrahedron Letters 40 (1999) 7735–7738

TETRAHEDRON LETTERS

Diastereofacial selectivity in ketene [2+2] cycloaddition to endocyclic enecarbamates bearing a chiral auxiliary. Synthesis of the (−)-Geissman–Waiss lactone

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Received 30 June 1999; revised 3 August 1999; accepted 4 August 1999

Abstract

The diastereofacial selectivity of enecarbamates bearing a chiral auxiliary was evaluated for the [2+2]cycloaddition with dichloroketenes. Diastereofacial selectivity ranged from zero (bornyl and menthyl) to 60% (Greene's auxiliary and 8-phenylmenthyl). Chromatography separation of the diastereomeric azacyclobutanones derived from the 8-phenylmenthyl enecarbamate permitted an enantiodivergent synthesis of the (−)-Geissman–Waiss lactone, a key intermediate in the synthesis of necine bases.

Keywords: chiral auxiliaries; enecarbamates; ketenes; Geissman–Waiss lactone.

Chiral auxiliaries (CA) have been extremely useful agents to incorporate asymmetry into intermediates in organic synthesis.[1] In our pursuit to apply endocyclic enecarbamates in the synthesis of nitrogen containing heterocycles we were faced with the challenge of introducing asymmetry to reactions involving simple enecarbamates bearing no stereogenic centers.[2] Diastereoselection carries the potential advantage of separation of the diastereomeric products which can be used to eventually produce both enantiomers of the desired product (Scheme 1). In the present study we evaluated the diastereoselectivity imparted by chiral auxiliaries on [2+2] cycloaddition of five-membered endocyclic enecarbamates and its application to the enantioselective synthesis of useful intermediates. This latter objective is illustrated with the enantioselective preparation of the levorotatory form of the Geissman–Waiss lactone, a key intermediate in the synthesis of several necine bases.[3]

Two scenarios would be best for the above strategy: (1) diastereoselectivity is high and we obtain mostly or entirely one stereoisomer; (2) diastereoselectivity is low, but the stereoisomers are readily separated. A complicating factor that adds more complexity to the proposed diastereoselective process is the presence of two distinct populations of rotational isomers due to the N–CO bond of carbamates.[4]

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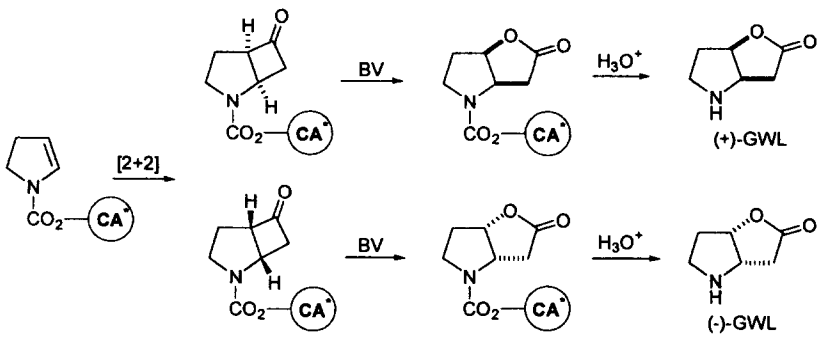
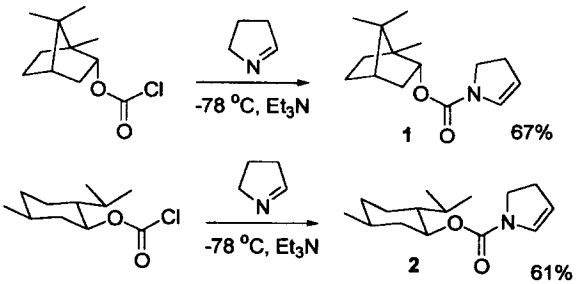
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01638-X



Scheme 1. Strategy for the enantiodivergent synthesis of the Geissman–Waiss lactone

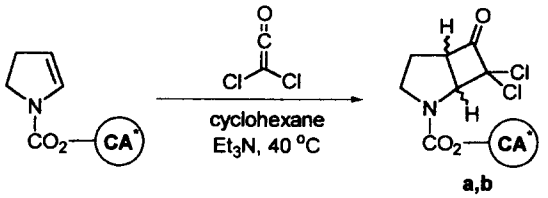
The enecarbamates **1** and **2** carrying (−)-*endo*-bornyl and (−)-menthyl as chiral auxiliaries were prepared in a straightforward manner by reacting the corresponding chloroformate (prepared from the alcohol with triphosgene in pyridine) with the trimer of 1-pyrroline (Scheme 2).[5]



Scheme 2.

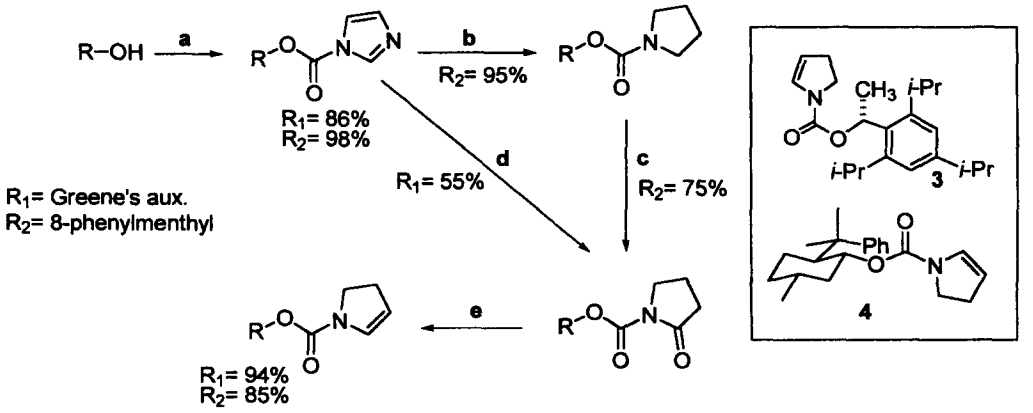
Enecarbamates **3** and **4** having the (*R*)-1-(2,4,6-triisopropylphenyl)ethanol (Greene's auxiliary)[6] and (−)-8-phenylmenthyl were prepared as described in Scheme 3. The longer sequences presented in Scheme 3 provided good overall yields of the enecarbamates[7] and were often more practical for preparing enecarbamates due to a somewhat difficult control in the quality of the unstable trimer of 1-pyrroline. During preparation of **3** we avoided exposing Greene's auxiliary to oxidative conditions, and thus the carbonylimidazole intermediate was reacted directly with 2-pyrrolidinone to afford the acyllactam, albeit in a maximum of 55% yield.

[2+2]Cycloadditions of enecarbamates **1–4** with dichloroketene are summarized in the Table 1.



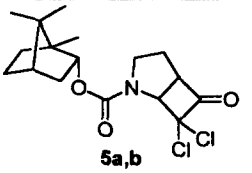
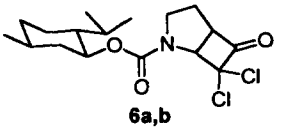
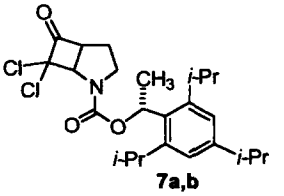
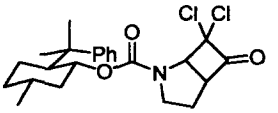
As expected, the yields for the [2+2] cycloaddition were consistently good. However, the stereoselectivities were relatively low. The ratio of stereoisomers vary from 1:1 to 1:4, and only products **8a** and **8b** could be separated by column chromatography. The presence of an aromatic ring proved crucial for attaining some stereoselectivity as exemplified by enecarbamates **3** and **4**.

Chromatographic separation of diastereomers **8a/8b** provided an opportunity to define the absolute sense of cycloaddition to enecarbamate **4**. This was done by converting the major diastereomer into the levorotatory stereoisomer of the Geissman–Waiss lactone **11** by a procedure used previously in our



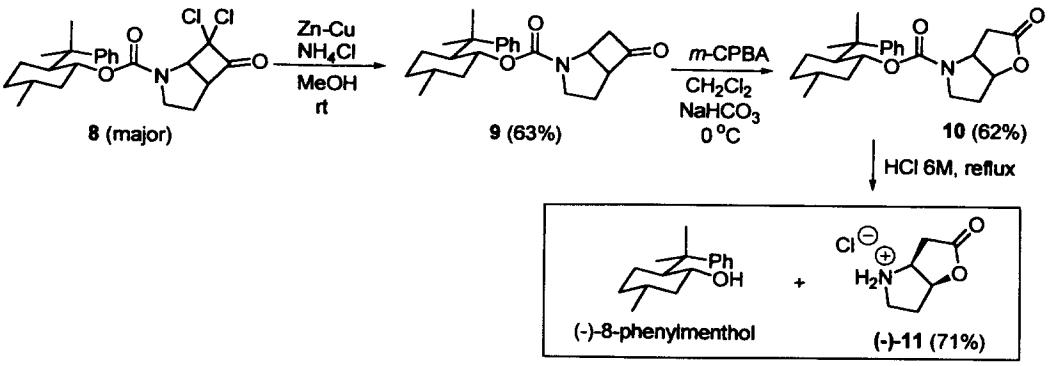
Scheme 3. Reagents and conditions. (a) 1,1′-Carbonyldiimidazole, CH_2Cl_2, rt; (b) pyrrolidine, rt; (c) $RuCl_3$ (cat.), $NaIO_4$, H_2O/EtOAc, 0°C to rt; (d) 2-pyrrolidinone, 85°C, 56 h; (e) 1. DIBAL-H, toluene, −78°C; 2. trifluoroacetic anhydride, 2,6-lutidine, then reflux for 20 min

Table 1

Enecarbamate	Product	Ratio of Stereoisomers	Yield
1	 **5a,b**	1:1	79%
2	 **6a,b**	1:1	84%
3	 **7a,b**	1:4	78%
4	 **8a,b**	1:4	88%

laboratories (Scheme 4).[8] All transformations proceeded uneventfully to provide (−)-**11** as a solid hydrochloride (the free amine is volatile and unstable). The specific rotation of **11** ($[\alpha]_D^{20}$ −45.0, 0.13, MeOH) was in good agreement to that described in the literature,[9] thus establishing the absolute configuration of **11** and pointing out the absolute facial diastereoselectivity dictated by the 8-phenylmenthyl auxiliary. Yields were not optimized due to the small scale for these reactions.

The sense of stereoinduction can be rationalized by a transition state in which the aromatic ring of the 8-phenylmenthyl group blocks more effectively one of the faces of the enecarbamate, therefore favoring the approach of dichloroketene from the *Si* face of the enamine moiety as depicted in Fig. 1. Charge



Scheme 4.

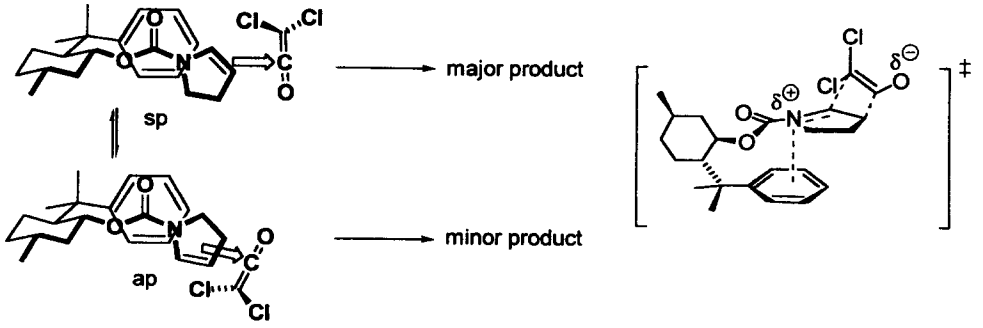


Figure 1.

stabilization and some π–π stacking may be playing a role in view of the enolate and *N*-acyl iminium character of the transition state.[10,11] It is also interesting to observe that the *ap* and *sp* conformations are equally populated at room temperature, as observed in the ^{13}C NMR spectrum of **4**.

Acknowledgements

We thank FAPESP for financial support, and CNPq and FAPESP for fellowships. We also thank Dr. Andrew Greene (Grenoble, France) for a gift of the (*R*)-1-(2,4,6-triisopropylphenyl)ethanol auxiliary.

References

1. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley: New York, 1995.
2. For asymmetric catalysis, see: Sugisaki, C. H.; Carroll, P. J.; Correia, C. R. D. *Tetrahedron Lett.* **1998**, *39*, 3413–3416.
3. Dai, W.-M.; Nagao, Y.; Fujita, E. *Heterocycles* **1990**, *30*, 1231–1261.
4. Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 2426–2427.
5. (a) Nomura, Y.; Ogawa, K.; Takeuchi, Y.; Tomoda, S. *Chem. Lett.* **1977**, 693–696. (b) Kraus, G. A.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 4791–4792.
6. Delair, P.; Kanazawa, A.; Azevedo, M. B. M.; Greene, A. E. *Tetrahedron: Asymmetry* **1996**, *7*, 2707–2710.
7. Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.*, in press.
8. Faria, A. R.; Matos, C. R. R.; Correia, C. R. D. *Tetrahedron Lett.* **1993**, *34*, 27–30.
9. Murahashi, S.-I.; Ohtake, H.; Imada, Y. *Tetrahedron Lett.* **1998**, *39*, 2765–2766. $[\alpha]_D$ –46.4 (c=1.43, MeOH)
10. For a review on π-stacking effects, see: Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, *5*, 475–479.
11. For the mechanism of cycloaddition, see: Tidwell, T. T. In *Ketenes*; John Wiley: New York, 1995; pp. 473–513.