



Pergamon

Tetrahedron Letters 41 (2000) 4339–4342

TETRAHEDRON
LETTERS

An efficient, asymmetric synthesis of (+)-euphococcinine[†]

Mark F. Mechelke and A.I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

Received 13 March 2000; accepted 18 April 2000

Abstract

The enantioselective synthesis of (+)-euphococcinine (**1**), a homotropane alkaloid, has been achieved in five steps from bicyclic lactam **5**. © 2000 Elsevier Science Ltd. All rights reserved.

Euphococcinine (**1**) was first isolated from an Australian coastal plant, *Euphorbia atoto*, in 1967.¹ Since then, it has also been found in the animal kingdom, specifically in the chemical defense systems of both ladybugs² and Mexican bean beetles.³ Along with its pentyl analog, (–)-adaline, which was also isolated from ladybug secretions,^{2,4} (+)-euphococcinine has been shown to be a potent feeding deterrent to both spiders and ants.

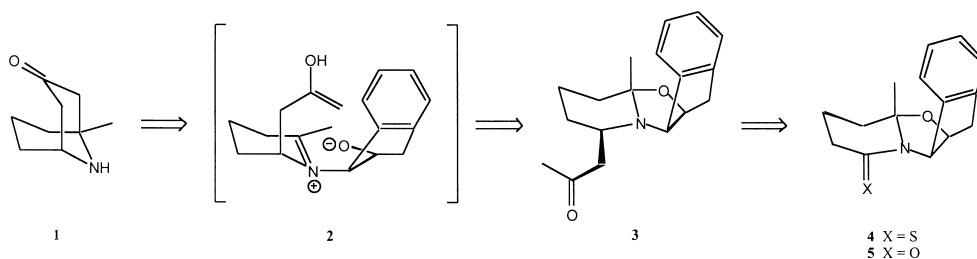
Although not particularly interesting from a biological standpoint, euphococcinine's unique bicyclic structure has drawn considerable synthetic interest. A variety of racemic syntheses of adaline and euphococcinine have been published in the past 40 years and most recently, two enantioselective syntheses of euphococcinine have been reported by Husson in 1992^{5a} and by Murahashi this year.^{5b} Due to our previous asymmetric routes to *cis*-2,6-disubstituted piperidines from chiral bicyclic thiolactams⁶ and our continuing effort in expanding the versatility of this chiral molecule, we anticipated that (+)-euphococcinine could be prepared in an asymmetric manner from an appropriately substituted 5,6-bicyclic lactam.

As shown retrosynthetically in Scheme 1, the preparation of (+)-euphococcinine (**1**) can be envisioned through an intramolecular Mannich reaction between the enol form of ketone **3** and the latent iminium ion **2** generated upon opening of the oxazolidine ring system. Ketone **3** may be accessed from bicyclic thiolactam **4** through an Eschenmoser sulfide contraction⁷ using bromoacetone as the electrophile followed by a diastereoselective reduction of the resultant α,β -unsaturated ketone.

In preliminary studies toward the preparation of ketone **3**, we employed the *gem*-dimethylphenylglycinol derived bicyclic lactam **6**.⁸ Treatment of the latter with Belleau's reagent⁹ provided

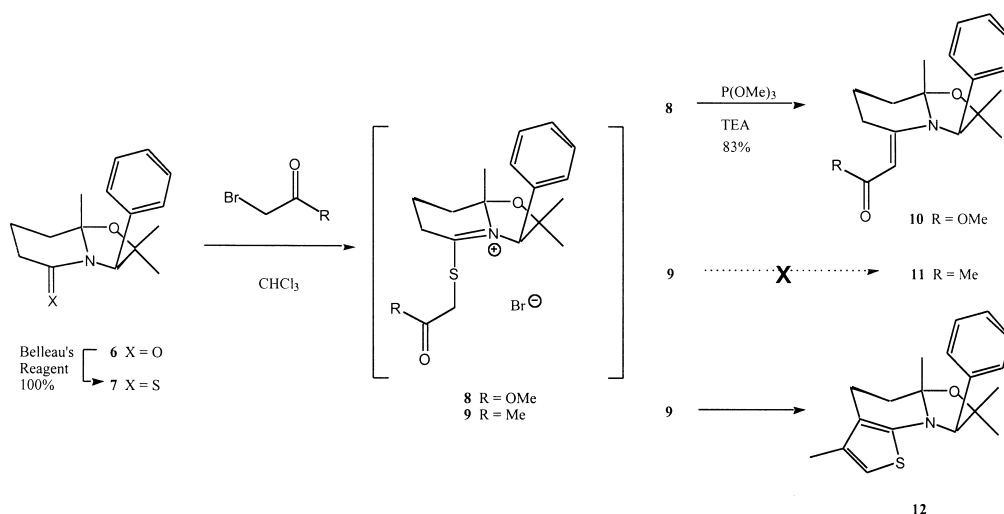
* Corresponding author.

[†] This paper is dedicated to Dr. Gurnes Jones for his long list of contributions to heterocyclic chemistry and on the occasion of his 70th birthday.



Scheme 1.

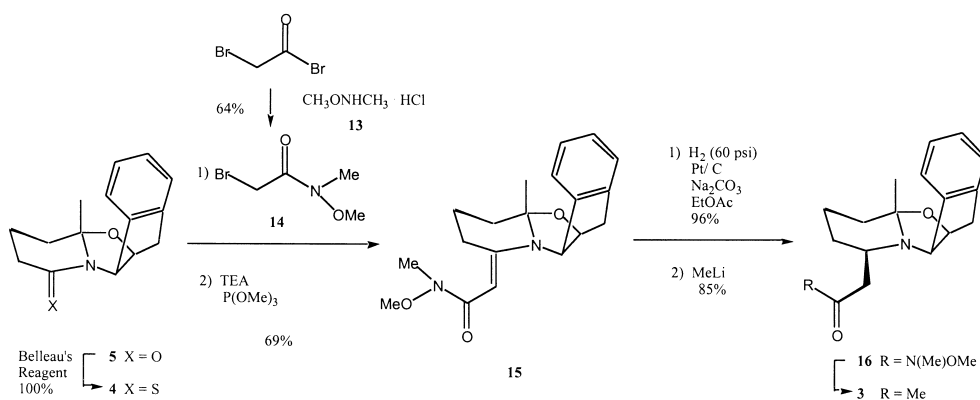
thiolactam **7** in quantitative yield. It was planned to convert thiolactam **7** into the vinylogous amide **11** in a single step via a sulfide contraction with bromoacetone. A similar transformation using methyl bromoacetate was previously applied in our group to prepare the corresponding vinylogous urethane **10** in an 83% yield.¹⁰ The addition of freshly prepared bromoacetone¹¹ to thiolactam **7**, however, resulted in the unexpected formation of thiophene **12**, instead of the desired vinylogous amide, **11** (Scheme 2). Similar thiophene products have been previously reported in sulfide contractions using α -bromoketones as substrates and are known to be a result of proton abstraction from the intermediate thioiminium salt (i.e. **9**).⁷



Scheme 2.

An alternative route considered to prepare **3** involved a sulfide contraction with the α -bromo Weinreb amide **14**. The latter was prepared from commercially available bromoacetyl bromide and *N,O*-dimethylhydroxylamine hydrochloride (**13**) in moderate yield (Scheme 3).¹² Furthermore, the chiral auxiliary in Scheme 3 was changed from a *gem*-dimethylphenylglycinol-derived bicyclic lactam (**6**) to a *cis*-1-amino-2-indanol derived lactam (**5**).¹³ Both of these chiral bicyclic lactams (**5** and **6**) were carried through the same sequence, but as will be seen (*vide supra*), the indanol derived lactam **5** gave the more satisfactory stereochemical and synthetic results.

Thiolactam **4**, prepared in quantitative yield from lactam **5** via Belleau's reagent,⁹ was treated with freshly prepared bromide **14** to afford the desired intermediate thioiminium salt, which, on

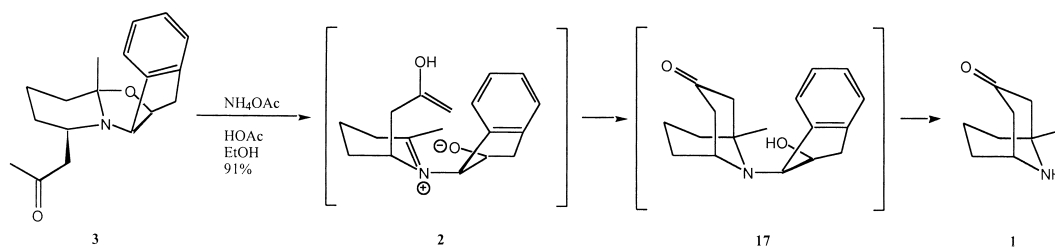


Scheme 3.

heating to reflux in triethylamine and trimethylphosphite, provided the sulfide contraction product **15** in 69% yield. Preliminary attempts at catalytic hydrogenation, using the conditions optimized for reduction of the corresponding methyl ester **10** (1 atm H_2 , Pt/C), led only to starting material. The unsaturated amide **15**, required 60 psi of hydrogen (approximately 4 atm) to produce a high yield of the saturated amide **16**. Once obtained, amide **16** was treated with MeLi at -78°C to afford ketone **3** in 82% yield over the two steps. At this point, the first major difference between the two chiral auxiliaries, (lactams **5** and **6**), was observed.¹⁴ In the case of the *gem*-dimethyl-phenylglycinol bicyclic lactam **6**, a 7:1 mixture of *exo:endo* diastereomers was observed after hydrogenation, whereas hydrogenation of lactam **5**, gave a single diastereomer of **16**.¹⁵ The poor diastereoselectivity observed with lactam **6** may be attributed to an increase in steric bulk on the *endo* face arising from the *gem*-dimethyl substituent.

To complete the synthesis of (+)-euphococcinine (**1**), an intramolecular Mannich reaction of **3** to **17** was required. A variety of acidic conditions were employed in an attempt to open the bicyclic ring system, thus exposing the latent iminium ion **2**, but all of these experiments met with failure, giving only recovered starting material or an unidentifiable mixture of products. However, the Mannich cyclization proceeded smoothly when amphoteric conditions were utilized. Ketone **3** was dissolved in 1:1 acetic acid:ethanol, treated with 10 equivalents of ammonium acetate, placed in a 75°C oil bath, and stirred overnight. After work-up (concentration followed by a $\text{Na}_2\text{CO}_3(\text{aq})/\text{CH}_2\text{Cl}_2$ extraction) and purification by column chromatography (9:1 CH_2Cl_2 :MeOH) the reaction mixture provided euphococcinine in 91% yield. Column chromatography (9:1 CH_2Cl_2 :MeOH), was necessary to afford (+)-euphococcinine (**1**). As shown in Scheme 4, this procedure not only transformed **3** into the natural product's bicyclic framework, but also resulted in concomitant loss of the chiral auxiliary to afford euphococcinine in a single step.

In conclusion, the synthesis of (+)-euphococcinine (**1**) was achieved in five steps, in 51% overall yield, from bicyclic lactam **5**. Spectral analysis (^1H and ^{13}C NMR, IR, and MS) of the synthetic sample was identical in all respects to the natural product.⁵ The $[\alpha]_D$ optical rotation of our sample averaged $+5.7$ (fluctuating between $+3.8$ and $+6.6$), yet was well within range of the literature value, $[\alpha]_D +6.0$.² Finally, it is interesting to note that when the synthetic sample of (+)-euphococcinine was treated with (*R*)-Mosher's acid chloride, no reaction was observed, however when it was treated with (*S*)-Mosher's acid chloride, euphococcinine was completely converted to a single Mosher amide. This observation not only proves that the present synthetic sample is



Scheme 4.

of high enantiomeric purity but also demonstrates that by simply treating synthetic racemic euphococcinine with (*R*)- or (*S*)-Mosher's acid chloride, kinetic resolution may potentially be achieved to access the single enantiomer.

Acknowledgements

The authors thank Merck for a post-doctoral fellowship (to M.F.M.) and the National Institutes of Health for financial support. We also thank Prof. Frank R. Stermitz for providing a natural sample of (+)-euphococcinine.

References

- Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1967**, *20*, 561.
- Brown, W. V.; Moore, B. P. *Aust. J. Chem.* **1982**, *35*, 1255.
- Eisner, T.; Goetz, M.; Aneshausley, D.; Ferstandig-Arnold, G.; Meinwald, J. *Experientia* **1986**, *42*, 204.
- Tursch, B.; Braekman, J.-C.; Daloze, D.; Hootele, C.; Losman, D.; Karlsson, R.; Pasteels, J.-M. *Tetrahedron Lett.* **1973**, 201.
- (a) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1992**, *57*, 4211, and references cited therein. (b) Murahashi, S.-I.; Sun, J.; Kurosawa, H.; Imada, Y. *Heterocycles* **2000**, *52*, 557.
- Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399.
- Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.
- Lemieux, R. M.; Devine, P. N.; Mechelke, M. F.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 3585.
- Lajoie, G.; Lépine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, *24*, 3815.
- Mechelke, M. F.; Meyers, A. I., unpublished results.
- Levene, P. A. *Org. Synth., Coll. Vol.* **1947**, *2*, 88.
- Nuzillard, J.-M.; Boumendjel, A.; Massiot, G. *Tetrahedron Lett.* **1989**, *30*, 3779.
- Senanayake, C. H.; Roberts, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Fredenburgh, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 3993.
- Another difference in lactams **5** and **6** was observed in the final cyclization step (**3** to **1**) where a 91% yield was achieved with **3** and only a 61% yield was obtained with the ketone derived from **6**.
- The *exo* stereochemistry was initially assigned based on results found in Ref. 6 and eventually proven by the synthesis of (+)-euphococcinine.