Pergamon

Tetrahedron Letters 42 (2001) 4633–4635

TETRAHEDRON LETTERS

Ring-closing metathesis of diolefinic oxazolidinones: a new access to tropanes and aminocyclitols

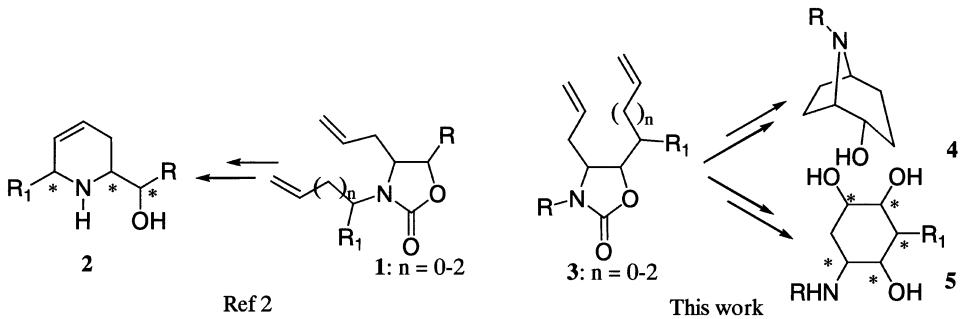
Claude Agami, François Couty* and Nicolas Rabasso

Laboratoire de Synthèse Asymétrique associé au CNRS, Université Pierre et Marie Curie, 4 place Jussieu, 75005 Paris, France

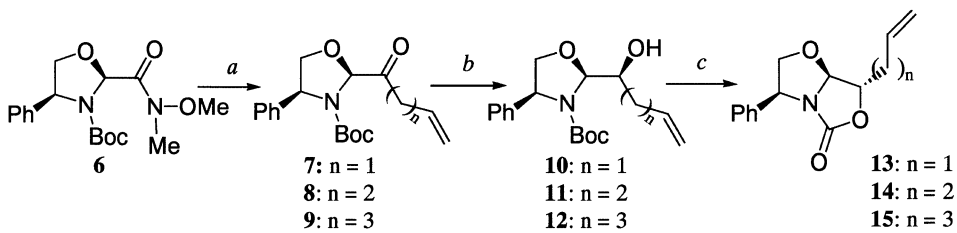
Received 30 April 2001; accepted 14 May 2001

Abstract—Ring-closing metathesis of diolefinic oxazolidinones prepared through *N*-Boc-2-acyl or α,β-epoxy oxazolidine methodology give stereodefined bicyclic oxazolidinones. The 5,6-membered bicyclic oxazolidinones are then converted into new aminocyclitols by diastereoselective dihydroxylation whereas their 5,7-membered bicyclic homologues are transformed into tropanic alkaloids through an aminocyclization step. © 2001 Elsevier Science Ltd. All rights reserved.

Owing to the introduction of efficient and easy to handle catalysts, ring-closing metathesis (RCM) has emerged as a powerful tool in organic synthesis, and this reaction is now recognized as the cornerstone of new strategies for the preparation of diverse classes of compounds.[1] In this rapidly expending area, we recently reported the use of RCM combined with the chemistry of *N*-Boc-2-acyloxazolidines for the synthesis of piperidinic alkaloids.[2] This work was based on the RCM of enantiopure diolefinic oxazolidinones of general structure **1**. We wish to report in this Letter new developments in this field, i.e. the synthesis and RCM of diolefinic oxazolidinones of type **3**, leading ultimately to tropanes **4** or aminocyclitols **5** after further transfor-



Scheme 1.



Scheme 2. *Reagents and conditions*: (*a*) allylmagnesium chloride (**7**), but-4-enylmagnesium bromide (**8**), pent-5-enylmagnesium bromide (**9**); (*b*) $NaBH_4$, EtOH, −78°C, 59% overall (**10**), 84% overall (**11**), 67% overall (**12**); (*c*) NaH, THF, reflux, 68% (**13**), 95% (**14**), 85% (**15**).

* Corresponding author. Tel.: (33) 1 44 27 30 13; fax: (33) 1 44 27 26 20; e-mail: couty@ccr.jussieu.fr

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)00830-9

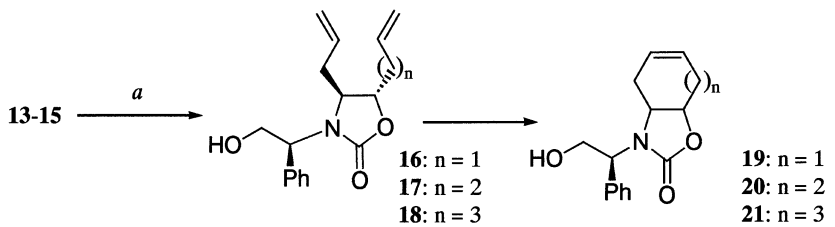
mations of the resulting bicyclic adducts. These molecules both belong to intensively studied families of molecules, because of the biological activity frequently displayed by their members (Scheme 1).

The synthesis of diolefinic oxazolidinones **3** started with Weinreb amide **6**, derived from (*S*)-phenylglycinol.[3] Treatment of this amide with the appropriate unsaturated Grignard reagent gave acyloxazolidines **7–9** in good yields. These ketones were then reduced with high (>90%) d.e.s using sodium borohydride at −78°C to afford α-hydroxy oxazolidines **10–12**. Transcarbamation of these compounds (NaH in THF) then gave bicyclic oxazolidinones **13–15**. This synthetic sequence was already reported for *ent*-**14**,[4] and shows similar yields and selectivities for the synthesis of *nor* and *homo* analogues **13** and **16**. However, the allyl-substituted oxazolidinone **13** was sensitive to basic medium and required optimized conditions (NaH, THF, 0.017 M solution, reflux, 0.5 h) to be produced efficiently in the last transcarbamation step (Scheme 2).

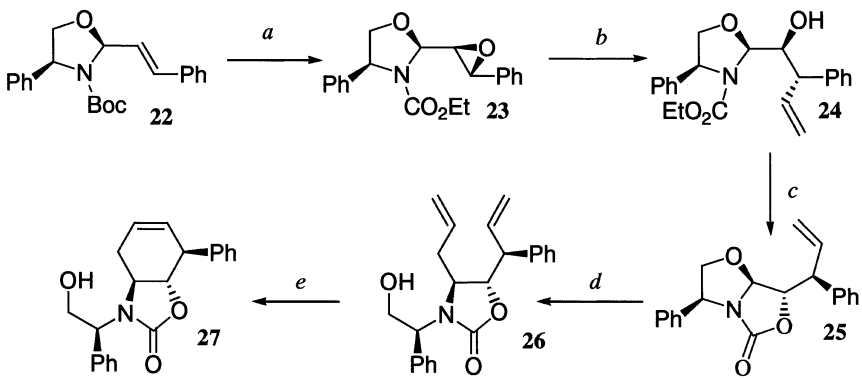
The nature of the Lewis acid used during the next allylation step was important to reach a good yield: treatment of olefinic oxazolidinones with $TiCl_4$ (**14**, **15**) or with $BF_3(OEt_2)$ (**13**) in the presence of allyltrimethylsilane gave *trans* diolefinic oxazolidinones **16–18** with high stereoselectivity,[4] and the latter were subjected to RCM in the presence of Grubbs' catalyst, in refluxing dichloromethane. Under these conditions, 5,6- and 5,7-membered bicyclic compounds **19** and **20** were obtained with good yields, whereas 5,8-membered **21** was not. This last result is not surprising owing to the well-known difficulty to build 8-membered rings by RCM.[5] (Scheme 3).

An alternative strategy was fruitful for the preparation of 5,6-membered bicyclic oxazolidinones. To this end, *N*-Boc alkenyloxazolidine **22** was epoxidized following our reported[6] two-step sequence, and the resulting epoxide **23** was treated with vinylmagnesium cuprate to give α-hydroxy oxazolidine **24** with high yield and total regioselectivity. This compound was then transformed into bicyclic oxazolidinone **25** upon treatment with NaH. The next allylation step was induced in this case by $BF_3(OEt_2)$ and smoothly provided *trans* bis-allylic oxazolidinone **26** with >90% de. Finally, RCM of **26** gave trisubstituted cyclohexene **27** (Scheme 4).

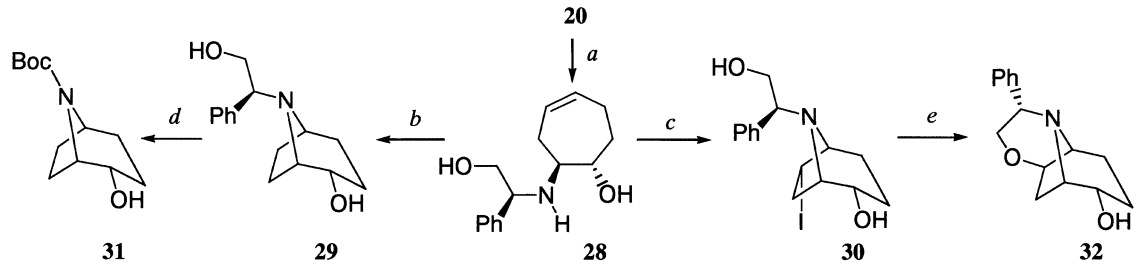
The chemistry of bicyclic oxazolidinones **20** and **27** was next investigated. First, base-catalyzed hydrolysis of **20** gave amino alcohol **28**, which was cyclized to tropane derivatives **29** and **30**. To this end, **28** was subjected to an aminomercuration followed by reduction of the intermediate organomercurial[7] or to a treatment with NIS,[8] respectively. It should be noted that no competitive nucleophilic opening of the transient mercuronium or iodonium ion by the hydroxyl moiety could be observed in these reactions. *N*-Debenzylation followed by *N*-Boc protection then gave **31** from **29**, whereas intramolecular etherification of **30** gave **32**. Since we have recently shown that the starting β-aminoalcohol used in these syntheses can be different from phenylgly-



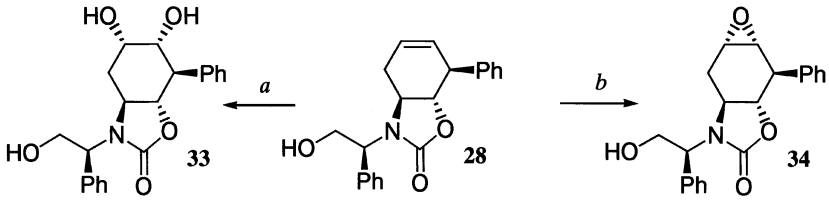
Scheme 3. *Reagents and conditions*: (*a*) $TiCl_4$ or $BF_3(OEt_2)$, allyltrimethylsilane, CH_2Cl_2, 66% (**16**), 80%(**17**), 77%(**18**); (*b*) Grubbs' catalyst, 3% molar ratio, CH_2Cl_2, 73% (**19**), 88% (**20**), 17% (**21**).



Scheme 4. *Reagents and conditions*: (*a*) i. NBS, DME/H_2O, ii. EtONa/EtOH, 72% overall; (*b*) $(vinyl)_2CuMgBr$, THF, −60°C, 87%; (*c*) NaH, THF, reflux, 76%; (*d*) $BF_3(OEt_2)$, allyltrimethylsilane, CH_2Cl_2, −78°C, 76%; (*e*) Grubbs' catalyst, 3% molar ratio, CH_2Cl_2, reflux, 91%.



Scheme 5. *Reagents and conditions*: (*a*) KOH, EtOH/H_2O, reflux, 76%; (*b*) i. $Hg(OAc)_2$, THF/H_2O, rt. ii. $NaBH_4$, NaOH, rt, 64%; (*c*) NIS, CH_2Cl_2, −78°C–rt, 48%; (*d*) H_2, Pd/C, AcOEt, Boc_2O, 78%; (*e*) NaH, THF, reflux, 50%.



Scheme 6. *Reagents and conditions*: (*a*) OsO_4 (cat.), NMO, acetone/H_2O, 50%; (*b*) TFAA, H_2O_2, CH_2Cl_2, 0°C, 61%.

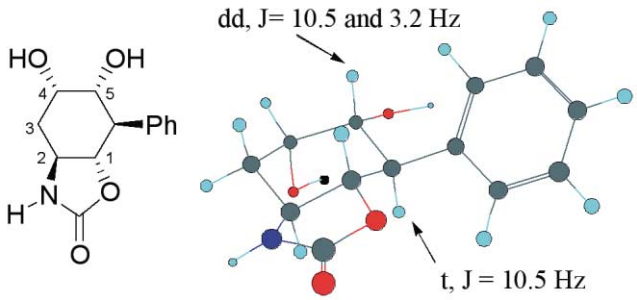


Figure 1.

cinol, this synthetic sequence provides a new entry to a large array of new tropanic alkaloids, being good candidates for their evaluation as cocaine analogues[9] (Scheme 5).

Analogous aminocyclizations were not operative when the amino alcohol resulting from the base-catalyzed hydrolysis of **27** was used as substrate. Nonetheless, the alkene moiety in **27** could be functionalized in a stereoselective way either by dihydroxylation, leading to **33** (d.e. >90%) or epoxidation, leading to **34** (d.e. 70%). In the latter case, the major stereoisomer could be isolated after flash chromatography (Scheme 6). The relative configurations of the newly created stereocenters in **33** and **34** were deduced from examination of their ^1H NMR data. For example, Fig. 1 shows the structure of the minimized conformation (AM1 calculation) of *N*-debenzylated **33**. The observed ^3J couplings, show unambiguously an axial orientation for the H_5 proton, therefore a *trans* relationship between hydroxyl substituent and phenyl ring is established.

Compound **33** is an aminocyclitol, and new synthetic routes for the preparation of members of this family are of high interest since they can provide potent glycosidase inhibitors.[10]

In conclusion, preliminary investigations of this synthetic strategy successfully gave new entries to important classes of bioactive compounds. Further work is in progress in our group in order to delineate its scope.

References

1. For recent reviews in this field, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron*, **1998**, *54*, 4413–4450; (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036–2056; (c) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75–89; (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.
2. (a) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2000**, *41*, 4113–4116; (b) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron* **2001**, in press.
3. Agami, C.; Couty, F.; Lam, H.; Mathieu, H. *Tetrahedron* **1998**, *54*, 8783–8796.
4. Agami, C.; Amiot, F.; Couty, F.; Dechoux, L.; Kaminsky, C.; Venier, O. *Tetrahedron: Asymmetry* **1998**, *9*, 3955.
5. Miller, S. J.; Kim, S. H.; Chen, Z. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109.
6. Agami, C.; Couty, F.; Venier, O.; Hamon, L. *J. Org. Chem.* **1997**, *62*, 2107–2113.
7. Barrelle, M.; Apparu, M. *Tetrahedron* **1977**, *33*, 1309–1319.
8. Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491–5501.
9. Singh, S. *Chem. Rev.* **2000**, *100*, 925–1024.
10. For some recent work in this field, see: (a) Pettit, G. R.; Melody, N.; Herald, D. *J. Org. Chem.* **2001**, *66*, 2583–2587; (b) De Almeda, M. V.; Figueiredo, R. M.; Dos Santos, H. F.; Da Silva, A. D.; Almeida, W. B. *Tetrahedron Lett.* **2001**, *42*, 2767–2769; (c) Sellier, O.; Van de Weghe, P.; Le Nouen, D.; Strehler, C.; Eustache, J. *Tetrahedron Lett.* **1999**, *40*, 853–856; (d) Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T. *Tetrahedron*, **2000**, *56*, 5819–5833.