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An Unexpected Oxidation in the Generation of Cyclopenta[*c*]piperidines by Ring-Closing Metathesis

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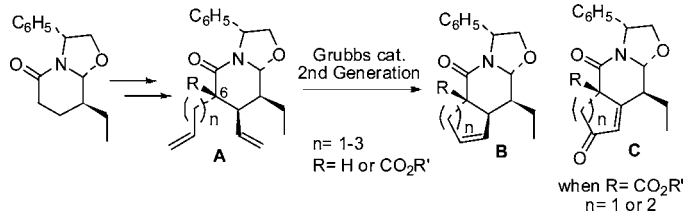
ABSTRACT



Ring-closing metathesis reaction of dienes A (*n* = 1, R= CO_2R') leads to fused cyclopentenones C instead of the expected cyclopentene derivatives B. RCM reaction of the other dienes A takes place satisfactorily, affording the expected fused cycloalkene derivatives B. Cyclohexene B (*n* = 2, R = CO_2R') also undergoes oxidation to the corresponding cyclohexenone C.

Chiral nonracemic amino alcohol-derived oxazolopiperidone lactams have proven to be versatile scaffolds for the enantioselective synthesis of piperidine-containing alkaloids and bioactive compounds.[1] These conceptually simple enantiopure molecules bear tactically versatile functionality that enables them to be elaborated into a great diversity of targets.

To further expand the scope of our enantiomeric scaffolding strategy[2] for the construction of enantiopure polysubstituted piperidine libraries, we devised a general route to highly substituted piperidines bearing a five-, six-, or seven-membered carbocyclic ring *cis* fused on the *c* side of the heterocycle. The key steps would be a stereoselective conjugate addition of a vinyl residue to an activated unsaturated lactam already bearing an alkyl substituent at the β-position of the piperidine ring, a stereoselective alkylation of the resulting β-oxo ester with unsaturated chains of different length, a ring-closing olefin metathesis (RCM) from the resulting dienes, and finally the reductive removal of the chiral inductor. We report here an unexpected oxidation after ring-closing metathesis in the cyclopenta- and cyclohexa[*c*]piperidine series.

Scheme 1 outlines the preparation of the starting dienes **3** from the known[3] lactam **1**. The conjugate addition of the vinyl group was accomplished in excellent chemical yield and complete *exo*-facial selectivity, *cis* with respect to the

(1) For reviews, see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569. (b) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1–8. (c) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873. (d) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198–8207. For more recent work, see: (e) Amat, M.; Pérez, M.; Minaglia, A. T.; Peretto, B.; Bosch, J. *Tetrahedron* **2007**, *63*, 5839–5848. (f) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431–4439. (g) Amat, M.; Santos, M. M. M.; Bassas, O.; Llor, N.; Escolano, C.; Gómez-Esqué, A.; Molins, E.; Allin, S. M.; McKee, V.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 5193–5201. (h) Amat, M.; Pérez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920–6923. (i) Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3348–3351. (j) Amat, M.; Fabregat, R.; Griera, R.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1794–1797. (k) Amat, M.; Gómez-Esqué, A.; Escolano, C.; Santos, M. M. M.; Molins, E.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1205–1211. (l) Amat, M.; Checa, B.; Llor, N.; Molins, E.; Bosch, J. *Chem. Commun.* **2009**, 2935–2937.

(2) Coombs, T. C.; Lee, M. D.; Wong, H.; Armstrong, M.; Cheng, B.; Chen, W.; Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2008**, *73*, 882–888.

(3) Amat, M.; Pérez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611–614.

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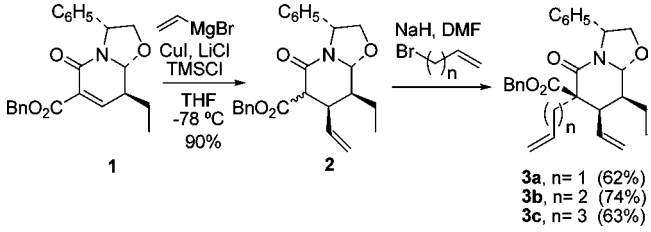
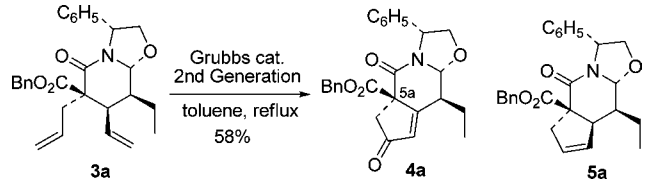
ethyl substituent, as a consequence of the stereoelectronic control.[4] A subsequent alkylation of the resulting mixture of C-6 epimeric lactams **2** with allyl bromide, 3-butenyl bromide, or 4-pentenyl bromide stereoselectively afforded dienes **3** as single stereoisomers.

Scheme 1. Enantioselective Synthesis of the Starting Dienes **3**



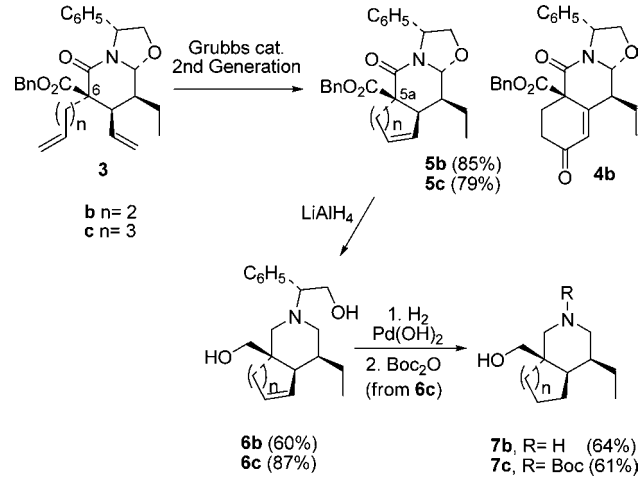
Quite surprisingly, RCM reaction[5] of lactam **3a** catalyzed by the second-generation Grubbs catalyst in refluxing toluene resulted in the formation of enone **4a** in 58% yield instead of the expected product **5a** (Scheme 2). A similar result was obtained when the reaction was carried out under Ar atmosphere. At lower temperatures (Ar, CH_2Cl_2, rt), most of the starting diene was recovered unchanged, and only trace amounts of enone **4a** were detected.[6] However, when the reaction was carried out in the dark under the last conditions, minor amounts of the expected cyclopentene derivative **5a** were detected (NMR) after careful flash chromatography (under Ar in the dark).

Scheme 2. Unexpected Oxidation in the Cyclopenta[*c*]piperidine Series



In contrast, RCM reactions took place satisfactorily, with no oxidation products being observed, from dienes **3b** (CH_2Cl_2, rt) and **3c** (toluene, reflux; no reaction was observed at rt in CH_2Cl_2 solution) to give in excellent yields the respective tricyclic lactams **5b** and **5c**, which were converted to substituted perhydroisoquinoline **7b** and perhydrocyclohepta[*c*]pyridine **7c** by $LiAlH_4$ reduction followed by catalytic debenzylation (Scheme 3). However, interestingly, refluxing (12 h) a toluene solution of **5b** in an open vessel resulted in a clean oxidation to give the fused cyclohexenone derivative **4b** in 77% yield. Fused cycloheptene derivative **5c** was recovered unchanged after a similar treatment.

Scheme 3. Ring-Closing Metathesis Reactions from Dienes **3b**,**c**



The formation of α,β-unsaturated ketones **4a** and **4b** from alkenes **3a** and **3b**, respectively, probably involves an initial allylic oxidation of the methine carbon at the piperidine 4-position followed by an allylic rearrangement and a subsequent oxidation. This unexpected aerial oxidation can be rationalized by considering that the change of the sp^3 hybridation of the piperidine 4-carbon to sp^2 relieves the strain in these highly congested *trans*-fused systems, in particular in the cyclopentene **a** series, which suffer from strong 1,3-diaxial interactions between the bulky substituent at the quaternary C-5a position and the ethyl substituent.[7]

In order to confirm this interpretation, we decided to study similar RCM reactions from dienes lacking the quaternary C-6 center. To remove the alkoxycarbonyl substituent without affecting the two carbon−carbon double bonds in the alkene moieties required for the RCM reaction, we prepared *tert*-butyl esters **13**. This was performed, as outlined in Scheme 4, following a synthetic route similar to that previously developed in the above benzyloxycarbonyl series.

In this series, the stereoselectivity of the conjugate addition reaction was confirmed by converting the diastereoisomeric mixture of lactams **11** to a single oxazolopiperidone **12** by treatment with TFA followed by heating in refluxing toluene.

As could be expected from the above RCM reactions, and confirming the intermediacy of an allylic alcohol in the oxidation process, cyclization of diene **13a** (Ar, toluene, reflux) in the presence of the second-generation Grubbs catalyst (Table 1) resulted in the spontaneous oxidation of the initially formed alkene **16a** (not isolated), leading to a

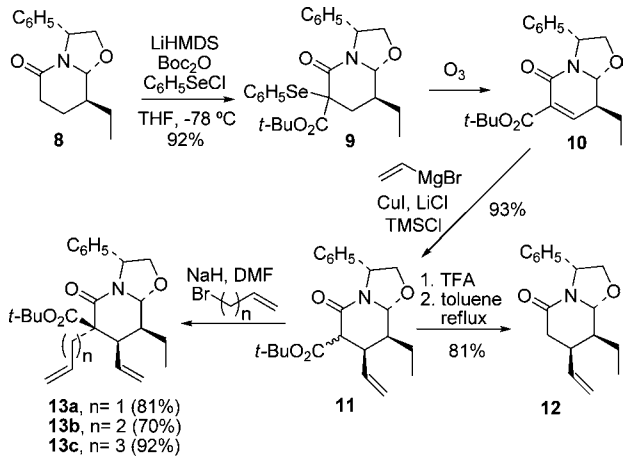
(4) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 221. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992; p 25.

(5) (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim 2003; volumes1−3. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.

(6) The residual oxygen in the solvent and/or the manipulation during workup and column chromatography purification could account for the observed oxidation .

(7) For a study of the effect of strain in the spontaneous oxygenation of cyclic olefins, see: Bartlett, P. D.; Banavali, R. *J. Org. Chem.* **1991**, *56*, 6043–6050.

Scheme 4. Synthesis of the Starting Dienes in the *tert*-Butoxycarbonyl Series



mixture of allylic alcohols **14a** (30%; nearly equimolecular mixture of C-7 epimers) and enone **15a** (30%) (entry 1).[6] As in the above cyclizations of **3b** and **3c**, cyclization of **13b** (entry 2) and **13c** (entry 3) took place in excellent yield to give the respective tricyclic lactams **16b** and **16c**.[8] Catalytic hydrogenation of **16b** and **16c**/**c**′ afforded the respective saturated lactams **17b** and **17c**.

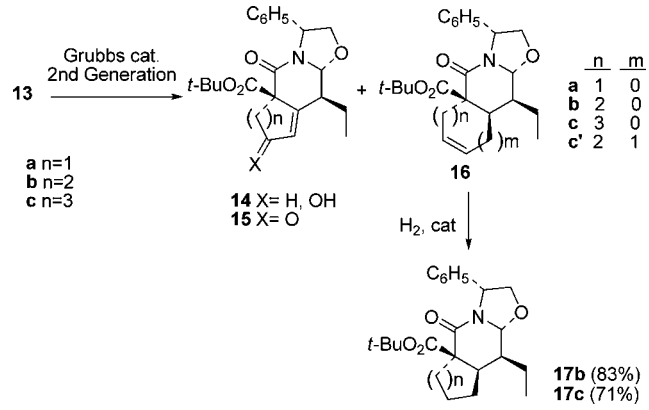
When the RCM reaction from diene **13b** was carried out in the absence of an inert atmosphere (Table 1, entries 4 and 5), mixtures of the cyclohexene derivative **16b** and allylic alcohols **14b** were obtained. As in the above benzyloxycarbonyl series, **16b** was oxidized (87% yield) to the corresponding enone **15b** by heating at reflux in toluene solution. Under these conditions, alcohol **14b** was similarly oxidized (85%) to enone **15b**. No oxidation was observed after heating **16c**/**c**′.

Removal of the C-6 *tert*-butoxycarbonyl group from **13a**−**c** was accomplished by treatment with TFA followed by heating of the resulting keto acids in refluxing toluene to give in good yields approximately 4:1 mixtures of the respective *all-cis* trisubstituted piperidine derivatives **18a**−**c** and the corresponding C-6 epimers.

As we had assumed, *cis*-fused dienes **18a**−**c** underwent RCM reaction to give the corresponding *cis*-fused cycloalkenes **19a**−**c** in excellent yields (Scheme 5). The reactions were carried out at rt in CH_2Cl_2 solution in series **a** and **b** but in refluxing toluene in the seven-membered ring series **c**.[8] In no case were oxidation products detected, even when the reactions were carried out in the absence of an inert atmosphere. As outlined in Scheme 5, tricyclic lactams **19** were easily converted in excellent overall yield to the enantiopure perhydrocycloalka[*c*]pyridine derivatives **23a**−**c**,

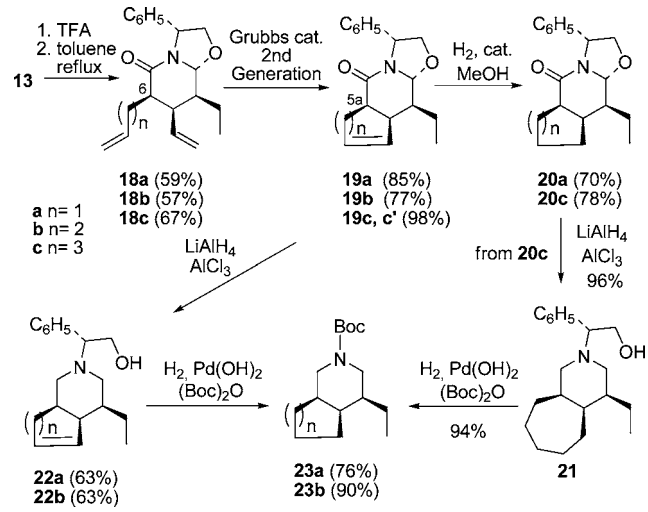
(8) A double-bond isomerization was observed in the cyclohepta series to give mixtures of **c** and **c**′ isomers. For related isomerizations in RCM reactions, see: (a) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672–7687. (b) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161. (c) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706–2714.

Table 1. Ring-Closing Metathesis Reactions from Dienes **13**



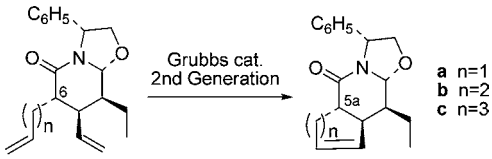
entry	diene	solvent	argon	product (%)
1	**13a**	toluene, Δ	yes	**14a** (30), **15a** (30)
2	**13b**	CH_2Cl_2, rt	yes	**16b** (84)
3	**13c**	toluene, Δ	yes	**16c**,**c**′ (95)
4	**13b**	CH_2Cl_2, rt	no	**14b** (24), **16b** (60)
5	**13b**	toluene, Δ	no	**14b** (34), **16b** (41)

Scheme 5. Ring-Closing Metathesis Reactions in the *Cis*-Fused Series



thus further illustrating the synthetic potential of phenylglycinol-derived oxazolopiperidone lactams in the generation of enantiopure polysubstituted piperidine libraries. To confirm that the different behavior of diene **18a** in comparison with dienes **3a** and **13a** in the RCM reactions can be attributed to the absence of the C-6 alkoxycarbonyl substituent rather than to the different ring fusion in the resulting tricyclic alkenes (*trans* in **5** and **16** but *cis* in **19**), we also studied the RCM reactions from 6-*epi*-**18a**−**c**, which would lead to *trans*-fused cycloalka[*c*]piperidines (Scheme 6). Oxidation was not observed in this series either, and the tricyclic *trans*-fused cycloalkenes 5a-*epi*-**19a**−**c**[8] were isolated in excellent yields.

Scheme 6. Ring-Closing Metathesis Reactions in the *Trans*-Fused Series



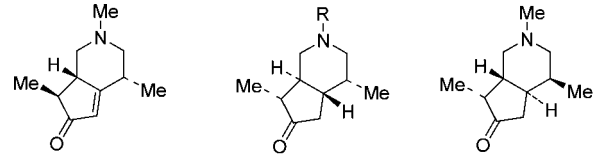
6-*epi*-**18**

5a-*epi*-**19a** (80%)
5a-*epi*-**19b** (96%)
5a-*epi*-**19c,c'** (71%)

The above results demonstrate that the unexpected oxidations here reported are a consequence of the strain present in the *trans*-fused cycloalka[*c*]piperidine systems resulting from the RCM reactions. The oxidation occurs spontaneously in the highly strained cyclopenta fused derivatives, only after refluxing in toluene solution in the absence of an inert atmosphere in the less congested perhydroisoquinoline series, but it was not observed in the cyclohepta[*c*]piperidine derivatives.

Taking into account that the 6-oxocyclopenta[*c*]piperidine skeleton is present in a stereochemically diverse group of monoterpenoid pyridine alkaloids derived from iridodial-like presursors[9] (Figure 1), starting from appropriate lactams the unexpected oxidation reported here could provide a versatile enantioselective route to these alkaloids.[10]

(9) (a) Dickinson, E. M.; Jones, G. *Tetrahedron* **1969**, *25*, 1523–1529. (b) Harris, G. H.; Fixman, E. C.; Stermitz, F. R.; Castedo, L. *J. Nat. Prod.* **1988**, *51*, 543–548. (c) Lins, A. P.; Felicio, J. D. *Phytochemistry* **1993**, *34*, 876–878. (d) Kam, T.-S.; Yoganathan, K.; Wei, C. *J. Nat. Prod.* **1997**, *60*, 673–676.



(-)-Tecomanine

(-)-Kinabalurine B R= Me
(+)-Kinabalurine C R= H

(+)-Kinabalurine E

Figure 1. Alkaloids with a 6-oxocyclopenta[*c*]piperidine skeleton.

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Supporting Information Available: . Experimental procedure for the RCM reaction from **3a** and ^{1}H NMR and ^{13}C NMR spectra for compounds **3a**−**c**, **4a**,**b**, **5b**,**c**, **7b**,**c**, **13a**−**c**, **14a**,**b**, **15a**,**b**, **16b**,**c**, **18a**−**c**, 6-*epi*-**18a**−**c**, **19a**,**b**, 5a-*epi*-**19a**−**c**, **20c**, and **23a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Only one enantioselective synthesis of (+)-tecomanine has been reported: Kametani, T.; Suzuki, Y.; Ban, C.; Honda, T. *Heterocycles* **1987**, *26*, 1491–1493.