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Communication

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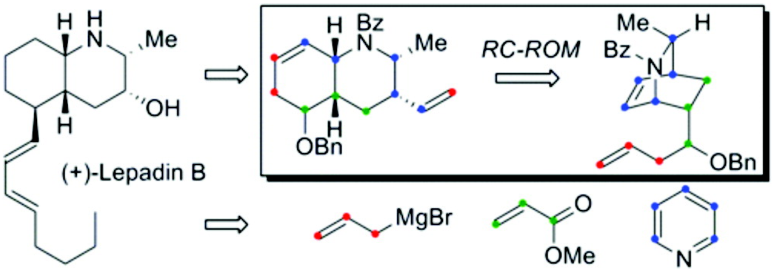

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COMMUNICATIONS

Total Synthesis of (+)-Lepadin B: Stereoselective Synthesis of Nonracemic Polysubstituted Hydroquinolines Using an RC-ROM Process

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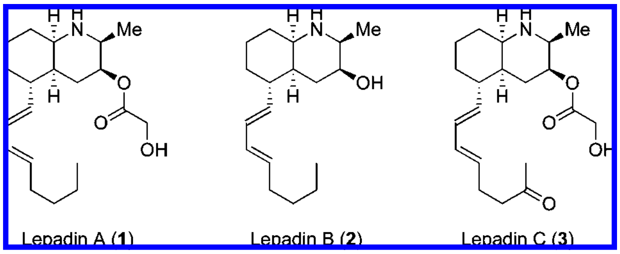
Lepadins are members of a growing family of natural products possessing a *cis*-fused decahydroquinoline subunit in which five stereogenic centers are included.[1] Lepadin A (**1**) and B (**2**), which were isolated from the tunicate of *Clavelina lepadiformis*,[1a,] have been shown to exhibit significant *in vitro* cytotoxicity against several human cancer cell lines.[1] In addition, Tsuneki et al. recently identified lepadin B as a potent blocker of neuronal nicotinic acetylcholine receptors (nAChR's) α4β2 and α7.[2] As nAChR's have been implicated in several neurological disorders including nicotinic addiction, epilepsy, and Parkinson's and Alzheimer's diseases, lepadin B could represent a new lead for the development of nicotinic-based therapies. These structural and biological features motivated research groups worldwide to address the synthetic question of lepadin B, culminating to date in three asymmetric total syntheses based on enzymatic[3a,b] and chiron[3c−f] approaches.[3g]

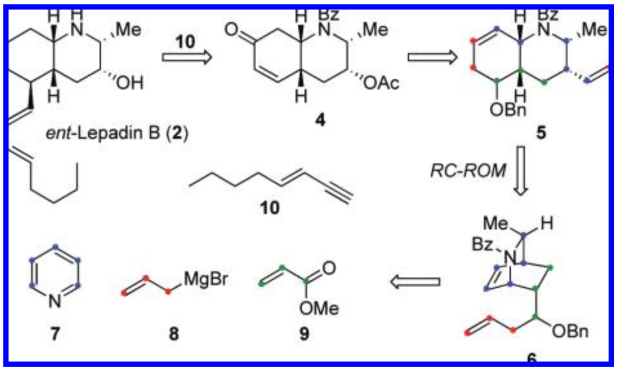


Over the past decade, alkene metathesis has emerged as a powerful tool in organic synthesis for the rapid access of structural complexity.[4] Particularly, alkene metathesis-induced molecular rearrangements have been widely explored and successfully applied as atom economic strategies[5] for natural product syntheses.[4c] Among these, ring-opening/ring-closing metathesis (ROM-RCM) processes involving bicyclo[2.2.1]heptenes were extensively studied for the synthesis of all-carbon[6a−g] and heteroatom-containing [n.3.0]bicyclic systems.[6h−n] More recently, Phillips showed that the analogous bicyclo[2.2.2]octene can participate in such a metathesis sequence to produce [n.4.0] bicyclic systems including the *cis*-fused decaline structure.[7]

As part of our research program directed toward the stereoselective synthesis of polysubstituted piperidines,[8] we became interested in the hydroquinoline scaffold and elected to explore a new tandem metathesis as an atom economic strategy[5] for the formation of the *cis*-fused decahydroquinoline structures. Recognizing lepadin B as a valuable target to challenge our approach (*vide supra*), we embarked in the design of a synthetic strategy containing tandem metathesis chemistry as a key feature. Herein, we detail a stereoselective synthesis of chiral nonracemic *cis*-fused polysubstituted hydroquinolines and describe a new stereoselective total synthesis of *ent*-Lepadin B.

Our retrosynthetic analysis of lepadin B is outlined in Scheme 1. We identified enone **4** as a suitable Michael acceptor for late stage diastereoselective incorporation of the diene side chain. Retrosynthetic modification of enone **4**, including an enone transposition and a stereospecific Baeyer−Villiger oxidation at C-3 position, revealed polyhydroquinoline **5** containing all structural requirements for a tandem metathesis product.[7] Therefore, metathesis precursor **6** was a key synthon that could be rapidly accessed by applying our recently developed Diels−Alder based strategy.[8f] It is interesting to note that all atoms included in the lepadin B skeleton originate from inexpensive commodities, i.e. ring-opened pyridine **7**, readily available allyl Grignard reagent **8** as well as methyl acrylate **9** (Scheme 1).

Scheme 1. Retrosynthetic Analysis for Lepadin B



The synthesis begins with our regio- and diastereoselective, chiral auxiliary-based pyridine[8a] dearomatization. An *endo*-selective Diels−Alder cycloaddition then afforded azabicyclo[2.2.2]octene **12** (Scheme 2).[8f,9] It is noteworthy that these two steps positioned four of the five stereogenic centers included in lepadin B (Scheme 1). Alane reduction of the ester and amidine[8d] moieties, with *in situ* protection of the secondary amine, provided compound **13** in 47% yield for the three steps (92:8 er). This highly crystalline compound was easily recrystallized from EtOAc affording **13** in gram quantities with >99:1 er.[9] Finally, a three-step sequence from alcohol **13** provided the metathesis precursor **6** in 81% yield.

With diene **6** in hand, we began our exploration of the metathesis sequence. After extensive optimization (Table 1), we were delighted to find that submitting **6** to 2 mol % of Grubbs' catalyst second generation (**16**)[10] at 80 °C for 2 min afforded the desired rearranged product **5** in 79% yield (entry 6). It is noteworthy that no rigorous exclusion of air and moisture were required for this process, although such precautions gave a slight increase in the reaction yield (entry 12). In addition, performing the reaction under an ethylene atmosphere improved the catalyst's stability and prevented the formation of dimeric material[11] but significantly decreased the reaction rate (entry 13). Finally, we found that adding the catalyst portionwise was beneficial (entry 14) and particularly crucial for

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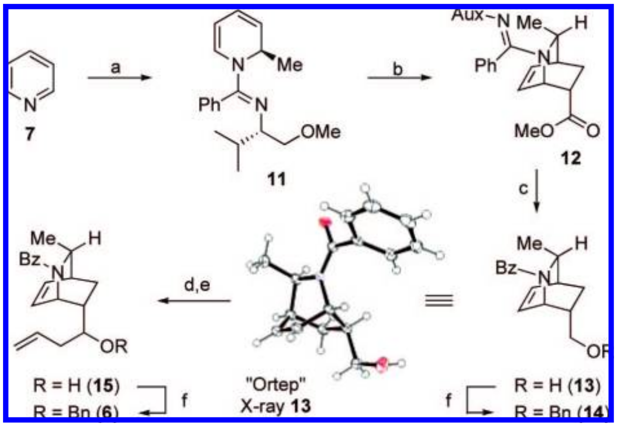
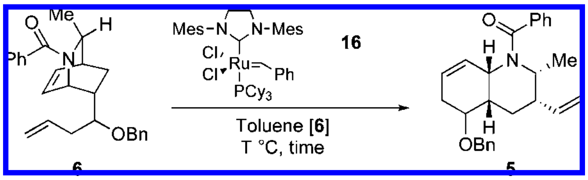
Scheme 2. Synthesis of Metathesis Precursors[a]



[a] Reagents and conditions: (a) (i) *N*-Bz-*O*-Me-L-valinol, **7**, Tf$_2$O, DCM, −78 °C → 0 °C; (ii) MeMgBr, −78 °C; (b) **9**, BF$_3$−Et$_2$O, toluene, 50 °C; (c) (i) LiAlH$_4$, AlCl$_3$, Et$_2$O/DCM, 0 °C → rt; (ii) BzCl, NaOH 2.5 N, 47% from **7** (3 steps); (d) **13**, (COCl)$_2$, DMSO, TEA, DCM, −78 °C; (e) AllylMgBr, DCM, −78 °C → rt; (f) BnBr, NaH, TBAI, DMF, rt, 98% for **14**, 81% for **6** (3 steps).

Table 1. Metathesis Reaction Optimization[a]



entry	16 (mol %)	[6] (M)	*T* (°C)	time (min)	yield[f] (%)
1	1.0	0.01	rt	24 h	72
2	1.0	0.01	60	6	74
3	1.0	0.01	80	2	74
4	1.0	0.01	reflux	2	74
5	5.0	0.01	80	2	77
6	2.0	0.01	80	2	79
7[b]	2.0	0.01	80	4	79
8	0.50	0.01	80	2	51
9[b]	0.25	0.01	80	4	29
10	2.0	0.05	80	2	71
11	2.0	0.10	80	2	65
12[c]	1.0	0.01	80	2	79
13[d]	1.0	0.01	80	2.5 h	62
14[b]	1.0	0.01	80	4	77
15[e]	2.5	0.01	80	30	75

[a] **16** is added at reported temperature to a solution of **6** (1 mmol) in commercially available toluene under an argon atmosphere. [b] Catalyst added in two portions. [c] Reaction performed under anhydrous conditions with degassed toluene (Ar atm). [d] Reaction performed under anhydrous conditions with degassed toluene (H$_2$C═CH$_2$ atm). [e] Reaction performed on 15 mmol of **6** with addition of catalyst **16** in three portions. [f] Mixture of diastereoisomers at C-5.

reliability on a multigram scale (entry 15). Relative stereochemistry of **5** was secured by X-ray analysis (Figure 1).

Two general mechanistic pathways could explain the formation of **5** from **6**, i.e., (A) ring-opening of the bicyclic system and ring-closure with the pending alkene (ROM-RCM) or (B) cross-metathesis of the ruthenium catalyst with the terminal alkene followed by a ring-closing/ring-opening metathesis sequence (RC-ROM) (Scheme 3). To gain insight into the main operative pathway, we submitted compounds **13** and **14**, both lacking their terminal alkene, to a wide range of metathesis conditions. We anticipated that, in the event of ROM being the first step of the catalytic cycle (mechanism A), various amounts of polymeric materials would be formed. Surprisingly, none of the conditions studied afforded any ring-opened products and all starting materials were completely recovered. This virtually absent reactivity of the internal alkene can be explained by a large steric demand on both faces of the π system, hence inhibiting catalyst approach. However, these results alone cannot entirely rule out mechanism A, since bicyclic compounds **13** and **14** may represent thermodynamic products in these conditions.[12]

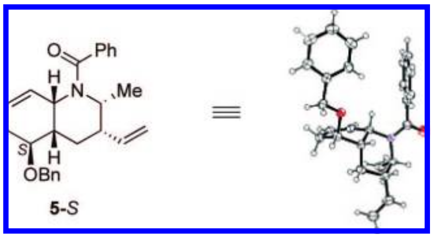
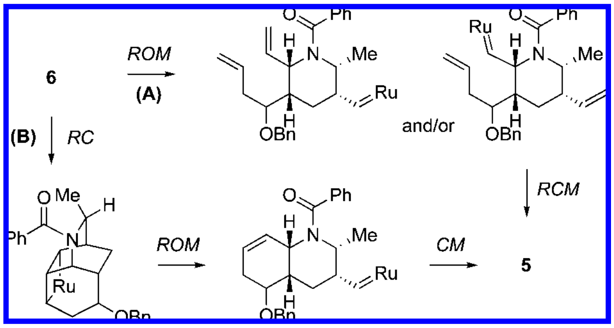
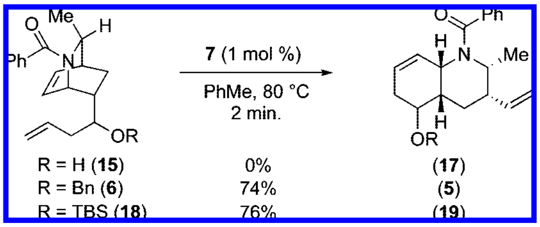


Figure 1. Relative stereochemistry: X-ray analysis of **5-*S***.

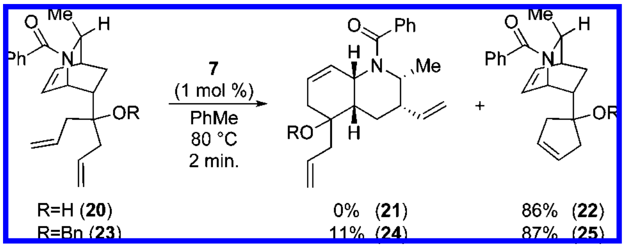
Scheme 3. Possible Mechanistic Pathways



Scheme 4. Proximal Hydroxyl Protecting Group Effect

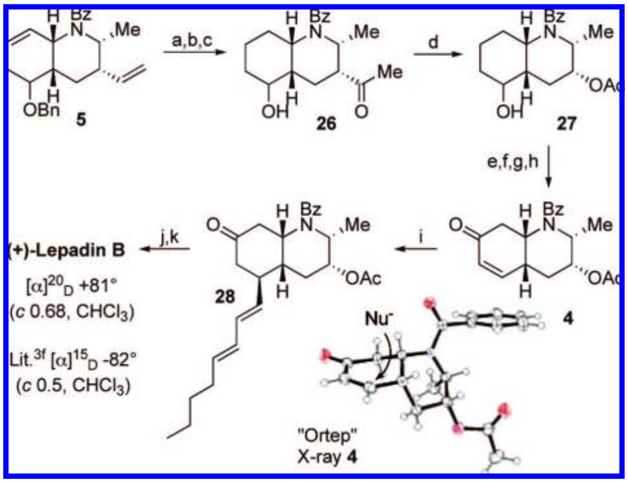


Scheme 5. Competitive Study



We, therefore, decided to probe the first step of mechanism B, i.e. the formation of a ruthenium carbene on the endo side chain. First, we examined the effect of the protecting group on the proximal secondary alcohol and rapidly realized that such protection was crucial to attain any conversion (Scheme 4). Then, we synthesized bis-allyl analogues **20** and **23**, hypothesizing that a five-member ring formation could compete with the expected rearrangement in the second step of mechanism B (RCM) (Scheme 5). Not surprisingly, free alcohol **20** failed in producing the desired rearranged product **21** (*vide supra*). However, the presence of the

Scheme 6. Total Synthesis of *ent*-Lepadin B[a]



[a] Reagents and conditions: (a) (i) $Hg(TFA)_2$, NaTFA, THF/H_2O (4:1), rt, 2 h; (ii) $NaBH_4$, NaOH 4.5 M; (b) Jones' reagent, acetone, rt, 1 h, 74% (2 steps); (c) H_2 (1 atm), Pd/C, MeOH, rt, 24 h; (d) TFAA, UHP, DCM, rt, 2 h, 69%; (e) IBX, toluene/DMSO (2:1), 80 °C, 15 h, 75%; (f) H_2O_2, KOH, THF/H_2O, rt, 2.5 min; (g) $H_2N{-}NH_2$, AcOH, MeOH, rt 2 h, 51% (2 steps); (h) TPAP, NMO, DCM, rt, 2 h, 75%; (i) **10**, $Cp_2Zr(H)Cl$, CuI−DMS, THF, 40 °C, 2 h, 76%; (j) $TsNHNH_2$; $NaBH_3CN$, $ZnCl_2$, MeOH, reflux, 2 h, 70%; (k) Me_3OBF_4, Na_2HPO_4, MeCN; $NaHCO_3$ aq.; K_2CO_3, MeOH, rt, 61%.

hydroxyl group did not impair the formation of a ruthenium carbene as cyclopentene **22** was obtained in 86% yield.

When compound **23** was treated under the same reaction conditions, cyclopentene **25** was isolated as the main product (87% yield), accompanied by 11% of the corresponding rearranged product **24**. The latter results are suggestive of a common ruthenium carbene involved in both mechanistic sequences leading to compounds **24** and **25**. Taken altogether, the absence of reactivity of compounds **13** and **14** and the large influence of the proximal hydroxyl group on the terminal alkene reactivity (Scheme 4), as well as the kinetically competitive cyclopentene formation over the expected rearrangement (Scheme 5), all support mechanism B as the main pathway for the formation of **5**.[13,14]

To complete the synthesis of *ent*-lepadin B, we turned our attention to the introduction of the oxygen at the C-3 position and sought a stereospecific Baeyer−Villiger oxidation as the obvious choice (Scheme 6). After extensive survey of reaction conditions, the required methylketone was obtained via a chemoselective oximercuration/reduction of the terminal alkene followed by the oxidation of the resulting alcohol using a Jones reagent. Hydrogenation of the remaining alkene concomitantly with hydrogenolysis of the benzyl ether provided ketone **26**. Cooper's conditions then produced the C-3 oxygenated, conveniently bis-protected compound **27**.[15] The free secondary alcohol was then oxidized to the corresponding enone[16] which was transposed following the Wharton three-step procedure (**4**).[17] The *trans*,*trans*-dienyl moiety was then introduced using Bergdhal's modification of the Lipshutz methodology with enyne **10** yielding 76% of **28** as a single stereoisomer.[18] Finally, a Wolff−Kishner reduction[19] and full deprotection[20] concluded an 18-step synthesis of *ent*-Lepadin B from pyridine **5**.

In conclusion, a new tandem metathesis reaction was presented for which an RC-ROM mechanism was experimentally supported. This process was successfully applied to the synthesis of *cis*-fused polyhydroquinolines enabling a new stereoselective total synthesis of lepadin B. We are further exploring the mechanism of the metathesis sequence and applying this methodology to the synthesis of other biologically interesting hydroquinolines. These results will be reported in due course.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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