Connecting Directed Ortho Metalation and Olefin Metathesis Strategies. Benzene-Fused Multiring-Sized Oxygen Heterocycles. First Syntheses of Radulanin A and Helianane

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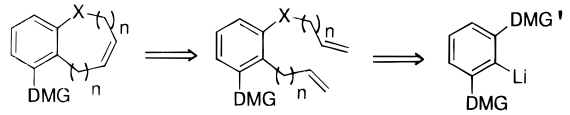
Despite its profoundly consequential foundation in polymer chemistry,[1] the olefin metathesis reaction has only recently enticed the attention of synthetic organic chemists, stimulating methodological studies[2] and total synthesis realizations.[3] While numerous medium-ring and macro ring carbocyclic and heterocyclic ring-closing metathesis (RCM) motifs have been reported,[1b,d] few benzannulated oxygen heterocycle constructs have been explored. Herein, we report the first cases of such RCM processes for various ring sizes $n = 7-9$, 12, and 14, demonstrating the synthetic link between RCM and the regiospecific directed *ortho* metalation (DoM) strategy,[4] potentially part of a broader program in the context of the conceptualization **1** → **2** → **3**, and tailor



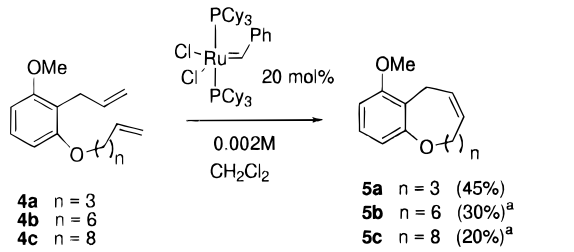
1 **2** **3**

X = CON-, O DMG, DMG' = CONHR, OMOM, OCONEt$_2$, NHt-BOC

this combined methodology to the first syntheses of radulanin A (**13c**) and (±)-helianane (**18**), natural products isolated from *Radula variabilis*[5] and *Haliclona fascigera*[6] respectively.

Scheme 1 summarizes exploration of ring-size effects on the RCM of the systematic series **4a**−**c**, prepared by DoM routes,[7] leading to annulated products **5a**−**c**. In consonance with observations by Grubbs,[8] higher yields were observed

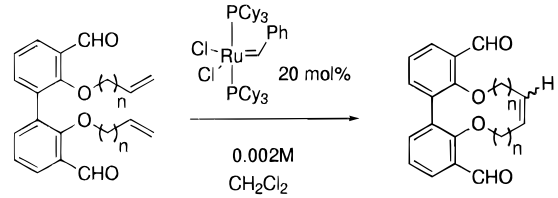
Scheme 1



4a n = 3
4b n = 6
4c n = 8

5a n = 3 (45%)
5b n = 6 (30%)[a]
5c n = 8 (20%)[a]

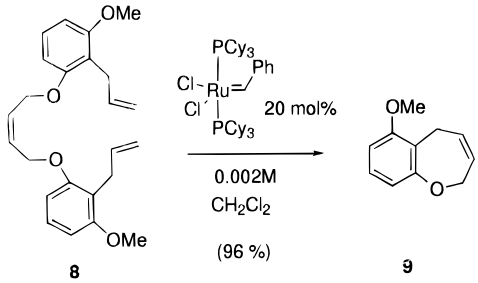
[a] Isolated as a mixture of *cis* and *trans* isomers



6a n = 3
6b n = 8

7a n = 3 (85%)[b]
7b n = 8 (80%)[b]

[b] geometry of double bond not determined



8 **9**

for $n = 3$ than for $n = 6$ and 8 due to greater conformational restraint in the former system. Attempts to improve yields by ethylene pretreatment[2a] were unsuccessful, and refluxing the reaction mixtures brought only marginal improvement in yields of **5b** and **5c**. In contrast, the biaryl systems **6a**,**b** underwent cyclization at room temperature without the use of ethylene to give macrocycle diethers **7a**,**b** in excellent yield (Scheme 1). Precursor **8**, which exhibits optional RCM reaction modes, afforded only the benzoxepin **9**, indicative of an entropic preference for seven-membered ring formation. Grubbs' ruthenium catalyst was used for all reactions; Schrock catalyst, in contrast to serving beneficially for a variety of reported cases,[2d] was ineffective in these RCM reactions.

The combined DoM−RCM strategy, **1** → **2** → **3**, finds effective expression in the first total syntheses of a calmodulin inhibitor, radulanin A (**13c**) (Scheme 2), and helianane (**18**) (Scheme 3). Thus, in the first of these, the readily constructed **10a**[9] was subjected to a DoM−transmetalation−allylation sequence to give **11a**, which upon acid-catalyzed MOM ether cleavage and O-allylation gave diallylated

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(7) Compounds **4a**−**c** were obtained from 3-methoxyphenol in four steps as follows: (1) MOMCl/CH_2Cl_2/NaOH/Bu_4NHSO_4; (2) *s*-BuLi/TMEDA/THF then $MgBr_2 \cdot Et_2O$ and allyl bromide; (3) HCl (aq)/THF/MeOH; (4) Cs_2CO_3/DMF/$CH_2{=}CH(CH_2)_nBr$ ($n = 3$, 6, and 8).

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(9) Compounds **10a** and **10b** were prepared from commercial 3,5-dimethoxybenzaldehyde in four steps, 63% and 54% overall yields, respectively, as follows: (1) PPh_3CH_2Ph/THF; (2) H_2/Pd−C; (3) NaSEt/DMF; (4) for **10a**, MOMCl/NaOH(aq)/CH_2Cl_2/Bu_4NHSO_4; for **10b**, $ClCONEt_2$/K_2CO_3/MeCN.

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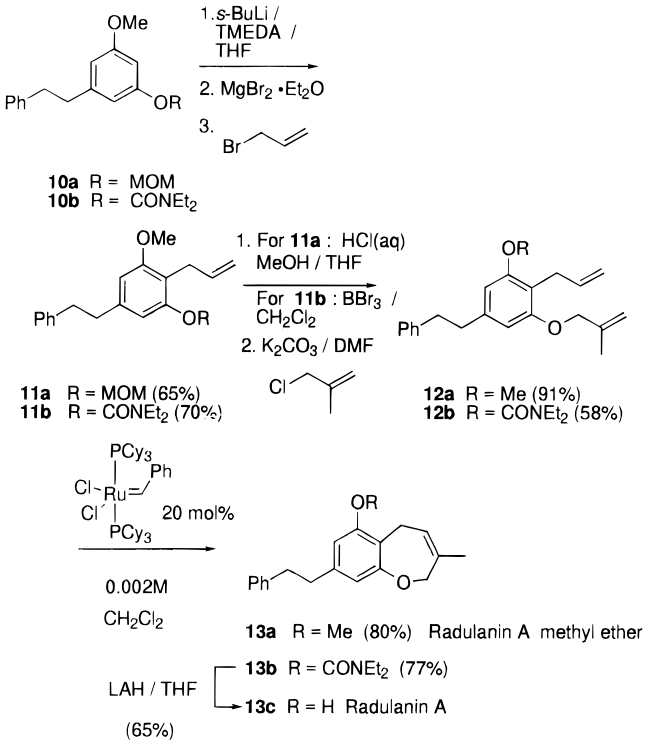
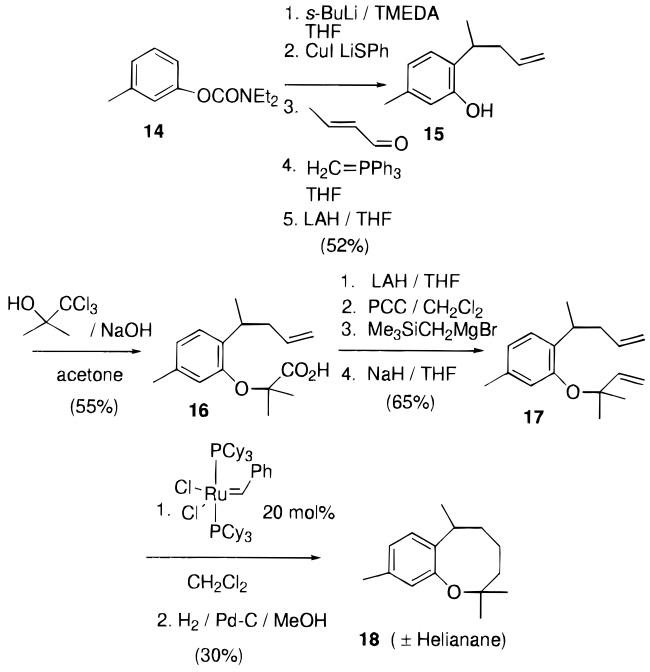
Scheme 2



Scheme 3



product **12a**. Upon treatment with 20 mol % of Ru-based catalyst (0.002 M/CH_2Cl_2/16 h/25 °C), **12a** afforded radulanin A methyl ether (**13a**).[5] Since demethylation of **13a** was compromised by the presence of the cyclic allylic ether, the synthesis of radulanin A (**13c**) was diverted to an approach starting with the *O*-carbamate **10b**. Following a sequence identical to that used for **13a**, sequential C- (→ **11b**) and O-allylation (→ **12b**) and RCM reaction afforded benzoxepine **13b**. Reduction using LAH completed the synthesis of radulanin A (**13c**)[5] (11 steps, 14% overall yield). Synthetic samples of **13c** and **13a** showed spectroscopic data (NMR) identical with those reported for the natural product and its methyl ether, respectively.[5]

The synthesis of helianane (**18**), a racemic natural product, was initiated from the *m*-cresol *O*-carbamate **14**, which, upon regioselective lithiation, transmetalation to the cuprate,[10] Michael addition, followed by Wittig olefination and reductive decarbamoylation, furnished the phenol **15** in 52% overall yield. In an interesting reaction discovered by Barghellini,[11] **15** was converted into the *gem*-dimethyl carboxylic acid **16**. A three-step sequence involving an ultimate Peterson olefination provided the RCM precursor **17**, which was subjected to Ru-mediated conditions as before followed by hydrogenation without intermediate isolation to give (±)-helianane (**18**) (9 steps, 6% overall yield). Its identity was established by direct comparison of spectroscopic data (NMR, MS) with an authentic sample.[6]

Multisized benzene-ring annulation processes **4a**,**c** → **5a**,**c** and **6a**,**b** → **7a**,**b** by advantageous combination of DoM and RCM protocols has been demonstrated, and its application to the synthesis of medium-sized ring natural products has been achieved. Extensions of the combined methodology to other directed metalation groups and modern synthetic processes may be envisaged and are in progress.

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Supporting Information Available: Experimental procedure for the cyclization of **4a** to **5a**, for the allylation of **10b**, for the synthesis of **15** and **16**, characterizations for **4a**, **5a**, **6a**, **7a**, **11b**, **12b**, **13a**, **15**, and **16**, and selected data for synthetic **13c** and **18** (7 pages).

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