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Tetrahedron Letters 45 (2004) 6283–6285
Tetrahedron Letters

A synthetic entry to 2,3-fused ring indole derivatives by ring-closing metathesis reactions

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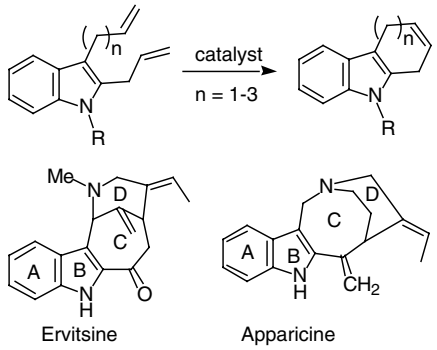
Received 25 March 2004; revised 14 June 2004; accepted 22 June 2004

Abstract—Six to eight-membered carbocycles and eight-membered azacycles fused to the 2,3-position of the indole ring, representing tricyclic substructures of several indole alkaloids, can be synthesized by RCM reactions from easily accessible dienic precursors.

Ring-closing metathesis (RCM) reactions[1] have become increasingly important in organic synthesis, and are now well-established processes for the construction of a great variety of carbo and heterocyclic systems.[2] In this context, considerable effort has been recently directed to the synthesis of benzo fused bicyclic compounds,[1,2] including quinolines,[3] chromenes[4] or larger rings.[5] However, there are relatively few examples that make use of RCM reactions for the synthesis of analogous indole derivatives,[6] a prominent class of heterocyclic systems found in many natural and medicinal compounds.[7] Our interest in the chemistry of indoles[8] led us to envisage RCM reactions as a useful tool for the construction of indole 2,3-fused carbo and azacycles,[9] which constitute structural arrangements present in some indole alkaloids such as ervitsine[10] or apparicine[11] (Scheme 1). In this Letter we report our preliminary results concerning this annulation procedure using easily accessible indole-containing diene precursors.



Scheme 1.

We planned to examine the feasibility of the RCM protocol in the carbocyclic series using 2-allylindoles (e.g., **3**–**5**, Scheme 2), which incorporate hydroxyalkenyl chains of different lengths at the 3-position. A similar approach had been used for the synthesis of 1,2-fused ring indole derivatives.[6c] Initially, we focused our attention on *N*-methyl derivative **3a**, which was prepared in 60% overall yield from the known 2-allylindole **1a**,[12] by Vilsmeier reaction with oxalyl chloride and DMF, followed by treatment of the resulting aldehyde **2a**[13] with vinylmagnesium bromide. However, this compound appeared to be very unstable and decomposed under chromatographic purification conditions. As this behaviour was probably associated with the presence of a 3-indolylmethanol moiety, we decided to place a strong electron-withdrawing group such as the benzenesulfonyl at the nitrogen of the starting allylindole **1b**.[14] Satisfactorily, Friedel–Crafts reaction with dichloromethyl methyl ether in the presence of $TiCl_4$ gave aldehyde **2b** (90% yield), which upon exposure to vinyl, allyl or 3-butenyl-magnesium bromide gave the stable RCM precursors **3b**, **4** and **5**, respectively, in 75–85% yield.

Considering the substitution pattern of dienes **3b**, **4** and **5**, their RCM reactions were next attempted using the commercially available ruthenium carbene catalyst $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (first generation Grubbs catalyst, Scheme 3). Ring closure of diene **3b** took place at

Keywords: Ring-closing metathesis; Indoles; Indole alkaloids.
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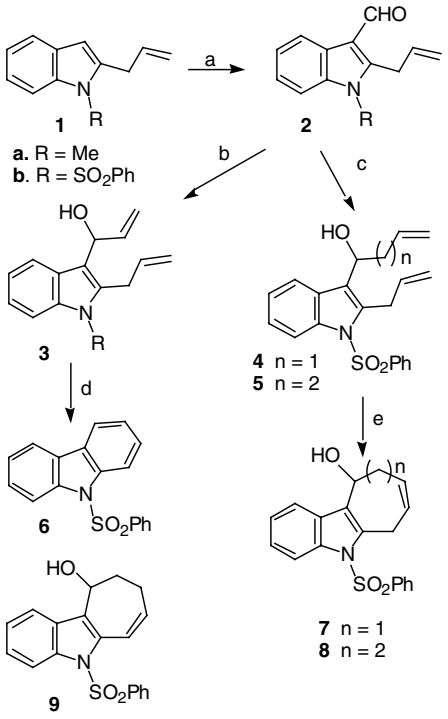
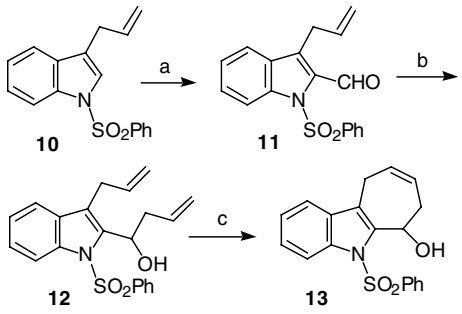
doi:10.1016/j.tetlet.2004.06.097



Scheme 2. Reagents and conditions: (a) For **2a**: $(COCl)_2$, DMF, CH_2Cl_2, rt, 8 h, 75%; for **2b**: Cl_2CHOMe, $TiCl_4$, CH_2Cl_2, −78 °C, 3 h, 90%; (b) $BrMgCH{=}CH_2$, THF, −78 °C to 0 °C, 3 h, 80% (**3a**, crude product), 75% (**3b**); (c) $BrMg(CH_2)_nCH{=}CH_2$, THF, −78 °C to 0 °C, 3 h, 82% (**4**), 85% (**5**); (d) 5 mol% $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, rt, 62%; (e) 10 mol% $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, reflux, overnight, 65% (**7**+**9**), 85% (**8**).

room temperature in dichloromethane to give the fully aromatic carbazole **6** (62% yield), coming from an additional in situ dehydration step. As anticipated, cyclizations of the higher homologous dienes **4** and **5** were a bit slower and they were better performed in refluxing dichloromethane. Under these conditions, **4** gave a mixture (variable ratio, 65% yield) of the expected cyclohepta[*b*]indole **7** and its isomer **9**, in which the double bond has moved to the indole α-position. The above isomerization to a 2-vinylindole system deserves comment as it might be mediated by the Grubbs catalyst or some species derived from it,[15,16] although a more conventional route cannot be discarded. In contrast, no isomerization was observed from **5**, which gave cycloocta[*b*]indole **8**[17] as the only product in the highest yield in this series (85%).

As depicted in Scheme 3, it was also possible to synthesize isomeric fused tricyclic indoles, for example, cyclohepta[*b*]indole **13**, through a similar synthetic sequence starting from 3-allylindole **10**.[14] In our hands, it was not possible to introduce the required formyl group by a Friedel–Crafts reaction but aldehyde **11** could be obtained in 60% yield by treatment of the 2-lithio derivative of **10** with DMF.[18] Reaction of aldehyde **11** with allylmagnesium bromide gave **12** (86% yield), which was submitted to the above RCM conditions to give **13** as the only product in 60% yield, again with no trace of isomerization product.

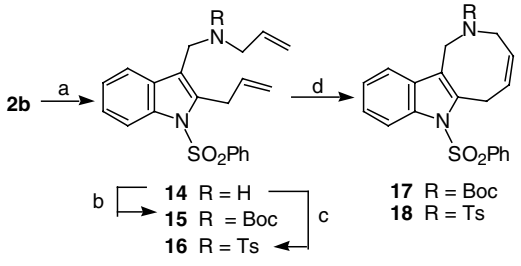


Scheme 3. Reagents and conditions: (a) *t*-BuLi, THF, −78 °C, 30 min, then, DMF, −78 °C to rt, 60%; (b) $BrMgCH_2CH{=}CH_2$, THF, −78 °C to 0 °C, 3 h, 86%; (c) 10 mol% $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, reflux, overnight, 60%.

The above success in the carbocyclic series, in particular the efficient construction of the eight-membered carbocycle **8**, led us to study RCM reactions from similar dienes incorporating a nitrogen in the tether linking the two olefinic moieties. Starting from aldehyde **2b**, a rapid access to the ABC ring substructure of apparicine through diallyl derivatives **15** or **16**, bearing different protecting groups at the aliphatic nitrogen, was envisaged (Scheme 4). Thus, reductive amination of **2b** with allylamine under mild conditions, followed by reaction of the resulting secondary amine **14** with di-*tert*-butyl carbonate gave carbamate **15**, which underwent cyclization under the above RCM conditions to give the azocino[4,3-*b*]indole **17** in 60% yield. As expected considering the precedents for RCM reactions from nitrogen compounds,[2] the *N*-tosyl derivative **16**, prepared by sulfonylation of **14**, was a better substrate as it led to **18**[19] in a higher yield (89%).

General experimental procedure: The ruthenium catalyst (10 mol%) was added under argon to a solution of the appropriate diene (**4**, **5**, **12**, **15** or **16**) in anhydrous CH_2Cl_2 (*c* 0.033 M), and the resulting mixture was refluxed overnight. The solvent was removed and the resulting residue was purified by flash chromatography (SiO_2, hexanes and hexanes–AcOEt) to give the corresponding tricyclic compounds.

In conclusion, we have described a synthetic approach to a range of 2,3-fused ring indole derivatives from sim-



Scheme 4. Reagents and conditions: (a) allylamine, AcOH, $NaBH(OAc)_3$, rt, overnight, 85%; (b) $(t\text{-}BuO)_2CO$, 4:1 MeOH–triethylamine, reflux, 4 h, 75%; (c) TsCl, Et_3N, CH_2Cl_2, rt, overnight, 70%; (d) 10 mol% $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, reflux, overnight, 60% (**17**), 89% (**18**).

ple precursors, using the Grubbs catalyst in the key ring-closing step. The extension of this work to the synthesis of indole alkaloids and related structures is currently under investigation.

Acknowledgements

Financial support from the 'Ministerio de Ciencia y Tecnología', Spain, and the 'Fondo Europeo de Desarrollo Regional' (FEDER) through project BQU2003-04967-C02-02 is gratefully acknowledged. We also thank the DURSI (Generalitat de Catalunya) for Grant 2001SGR00084.

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