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Synthesis of Muscothiazoles A and B: Critical Role of Methyl Group Substitution in RCM-Based Syntheses of Macrocycles

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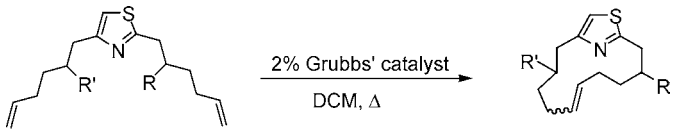
ABSTRACT



5a R = R' = H
5b R = H, R' = Me
5c R = Me, R' = H
5d R = R' = Me

7a 15%
7b 57%
7c 53%
7d 70%

Muscothiazoles A (2b) and B (2c) have been prepared by two approaches that differ in the order of assembly of the rings. Comparative studies show that substitution of the carbon chains in substrate 5 or 12 (respective precursors to 13-membered and 14-membered rings by RCM), even by a single methyl group, can have a profound effect on increasing the efficiency of the macrocyclization.

Musks are high-value components of perfumery products. (*R*)-(+)-Muscopyridine **1** (Scheme 1) is a naturally occurring macrocyclic musk isolated from the musk gland of the Tibetan or Himalayan male musk deer *Moschus moschiferus*.[1]

Scheme 1

(*R*)-(+)-Muscopyridine, **1**

2a R = R' = H
2b R = H, R' = Me
2c R = Me, R' = H
2d R = R' = Me

Racemic muscopyridine was first synthesized by Büchi et al.[2] and later by a number of other groups,[3] indicating its importance as a musk; the first total synthesis of the active enantiomer, (*R*)-(+)-muscopyridine, was reported in 1982,[4] but more recently, syntheses have been reported[5] with ring-closing metathesis as the key step. Structural isomers of muscopyridine have also been prepared[6] in studies on structure−odor relationships on this valuable family.

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(1) Schinz, H.; Ruzicka, L.; Geyer, U.; Prelog, V. *Helv. Chim. Acta* **1946**, *29*, 1524.
(2) Biemann, K.; Büchi, G.; Walker, B. H. *J. Am. Chem. Soc.* **1957**, *79*, 5558.
(3) (a) Tamao, K.; Kodama, S.-I.; Nakatsuka, S.; Kiso, Y.; Kumada, M. *J. Am. Chem. Soc.* **1975**, *97*, 4405. (b) Hiyama, T.; Shinoda, M.; Saimoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2747. (c) Sakane, S.; Matsurama, Y.; Yamamura, Y.; Ishida, Y.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 672. (d) Hadj-Abo, F.; Hesse, M. *Helv. Chim. Acta* **1992**, *75*, 1834.
(4) Utimoto, K.; Kato, S.; Tanaka, M.; Hoshino, Y.; Fujikura, S.; Nozaki, H. *Heterocycles* **1982**, *18*, 149.
(5) (a) Hagiwara, H.; Katsumi, T.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Org. Chem.* **2000**, *65*, 7231. (b) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308.
(6) Dubs, P.; Stüssi, R. *J. Chem. Soc., Chem Commun.* **1976**, 1021.

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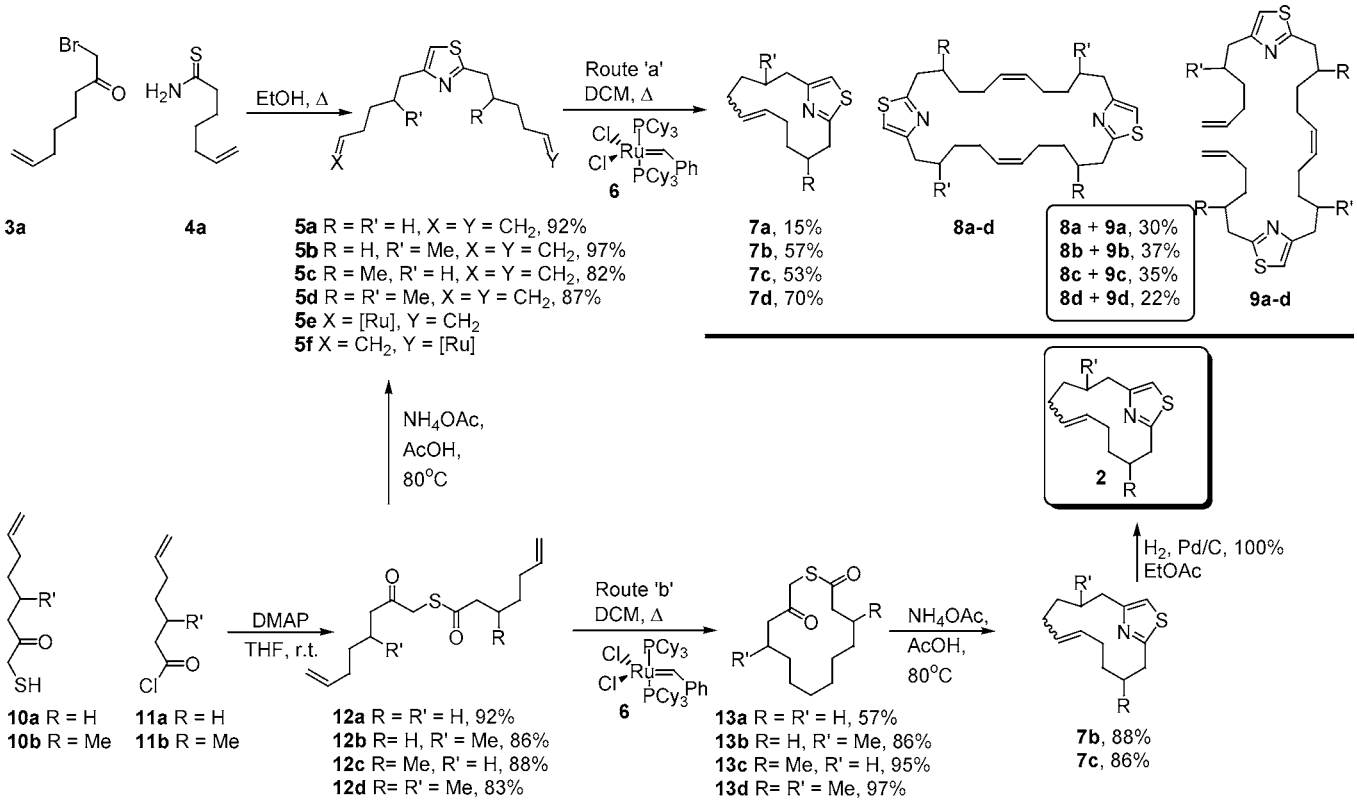
Scheme 2



In studies unrelated to those compounds, Kraft and Cadalbert[7] have noted a similarity between thiophene and benzene in terms of their olfactory effects, and this suggests that sulfur may generally replace a *Z*-configured alkene without greatly perturbing the odor characteristics of compounds. Since thiaterpenes are among the most powerful odorants known, a sulfur-containing counterpart to muscopyridine would be a useful and important target to synthesize. Hence, it was our aim to prepare "muscothiazoles A and B" **2b** and **2c**, sulfur-containing analogues of muscopyridine **1**, as potential new and powerful odorants with muscopyridine-like characteristics.

Two routes are readily seen that use ring-closing metathesis (RCM) as the key step to the muscothiazoles **2b**,**c** and their relatives **2a**,**d**. The first, route (a) (Scheme 2), assembles a disubstituted thiazole **5** as a substrate for RCM, while the second, route (b), proceeds by initial formation of a macrocycle (in this case, macrocycle **13**), followed by generation of the thiazole ring. Both routes were explored during this study.

Taking route (a) first, thiazole **5a** was prepared without difficulty by using the Hantzsch procedure[8] from bromoketone **3a** and thioamide **4a**. The related thiazoles **5b**−**d** were prepared by initially coupling the appropriate thiol **10a** or **10b** with acid chloride **11a** or **11b**.[9] Cyclodehydration of the product thioesters **12** in the presence of ammonium acetate in acetic acid[10] then led to the thiazoles **5b**−**d** in excellent yield (Scheme 2). This route to the thiazoles was chosen as it should later also conveniently provide macrocycles **13**, key intermediates in synthetic route (b).

Our first attempts[11] to form macrocycle **7a** by RCM on thiazole **5a** were fruitless. Addition of solutions of **5a** to a solution of Grubbs' catalyst **6** did not lead to detectable macrocyclic monomer **7a**, but instead to a complex mixture containing principally isomers of the cyclic dimer **8a** as well as a "deletion" product with mass 14 amu less than **8**, as indicated by GCMS. The deletion product must arise by isomerization of the (α,*ω*)-diene either in **5a** or the putative intermediate **9a** to its [α,(*ω*-1)] counterpart, prior to macrocycle formation. (A single isomer of **8a** is represented in the scheme, but we recognize that seven isomers of **8a** are possible; with **8b**−**d**, this number increases due to the chirality induced by methyl substitution. Representations of **8** are intended to represent all the isomers. With **9**, only the "head-to-tail" isomer is represented, but **9** should be taken also to represent the "head-to-head" and "tail-to-tail" isomers.)

Reports of compounds resulting from alkene isomerization are unusual[12] with Grubbs' catalyst **6**, although the more

(7) Kraft, P.; Cadalbert, R. *Synlett* **1997**, 600.
(8) Ciufolini, M. A.; Shen, Y. C. *J. Org. Chem.* **1997**, *62*, 3804.

(9) Although the racemic compounds **10b** and **11b** have been used here, their source is citronellic acid, both enantiomers of which are commercially available, so syntheses of enantiomerically pure samples of muscothiazoles are possible with use of this route.
(10) Dubs, P.; Stuessi, R. *Synthesis* **1976**, 696.
(11) Conditions: slow addition of solutions of **5a** [(i) DCM, 7 mM or (ii) DCM, 2 mM] to a solution of the catalyst **6** [(i) 0.25 equiv, 2.8 mM in DCM, Δ, 5 days *or* (ii) 0.2 equiv, 2.3 mM in DCM, Δ, 7 days].

reactive Schrock molybdenum catalysts[13] as well as the carbene-based catalysts are sometimes associated with isomerization.[13a,14]

We attributed the difficulty in forming the monomeric macrocycle **7a** to problems in attaining the desired proximity of the reactive termini of the side chains in **5e**,**f** (R = R′ = H) due to the 1,3-disubstitution of the thiazole.[15] Better conditions for the macrocyclization of **5a** were subsequently found (0.02 equiv of catalyst, DCM, Δ, 15 h), but this still provided a very poor yield of the monomeric macrocycle **7a** (15%), while affording the dimeric products in 30% yield. These products included **8a** as well as the linear dimer **9a** (as shown by GCMS). When thiazoles **5b**,**c** were subjected to similar reactions [under the same conditions], the reaction was much more successful (**5b** gave 57% of **7b** and 37% of **8b** + **9b**; while **5c** gave 53% of **7c** and 35% of **8c** + **9c**). These experiments showed that the presence of a single methyl group in either thiazole side chain greatly facilitated the formation of the monomeric products **7b**,**c**. The importance of substitution in the side chain was reinforced when the dimethyl substrate **5d** was reacted in like manner. This afforded the macrocycle **7d** in 70% yield, together with 22% of dimeric products **8d** + **9d**.

The control of substrate conformation in determining the success of RCM reactions has previously been discussed, particularly for medium-sized rings. Thus the role of conformational constraints in formation of eight-membered rings[16] was probed by a number of groups. Crimmins[17] and Taylor[12b] respectively extended the study to the role of vicinal acyloxy and acyloxymethyl groups and the corresponding silyloxy and silyloxymethyl groups in the synthesis of cyclic ethers. Linderman and co-workers probed[18] the effect of single substituents in eight-membered ring formation. They showed that while *tert*-butyl was not effective in permitting cyclization, the larger tributylstannyl group was effective. Hoveyda[19] presented an intriguing difference between an unsuccessful cyclization of an unsubstituted ether and a successful cyclization of the corresponding *p*-toluenesulfonamide. The success of the latter was attributed to the sterically demanding sulfonamide group. However, to our knowledge only one case[16d] has been reported where a small alkyl substituent, an ethyl group,[20] has dramatically affected the yield of cyclized product.[21] And yet, it is entirely reasonable that substitution by a small group could profoundly alter the efficiency of the reaction. In metathesis, the steric bulk of a metal−carbene group is considerable and so the energetic preference for the extended conformation of a side chain relative to a gauche one could be much larger than that for other reactions where smaller groups are present. Accordingly, even a single methyl substituent is likely to have a more profound effect in RCM than in most other reaction types.

Returning to the synthesis of the muscothiazoles, we were dissatisfied with the yields of **7** seen in route (a) and suspected that the efficiency of this route was limited by constraints imposed by the 1,3-disubstitution of the thiazole. Accordingly, the kinetically more favorable cyclization of the five-membered thiazole ring was deferred until after the macrocyclic core had been prepared, as in route (b). Macrocyclization[22] of **12a** afforded the monomer **13a** in a moderate 57% yield, while under identical conditions, monomethyl-substituted **12b** and **12c** respectively gave excellent 86% and 95% yields of the monomeric products **13b** and **13c**, respectively. Furthermore, the disubstituted **12d** afforded **13d** in 97% yield. The relative yields again attest to the importance of monosubstitution with a methyl group. In this case, we judge that the energetics for macrocyclization are not so difficult as with **5**, and hence the yield of the unsubstituted case **12a** is higher than that for **5a**; monosubstitution so increases the yield that the benefit of a second methyl substitution to yield is less pronounced.

The greater efficiency of route (b) compared to route (a) is reminiscent of studies on the synthesis of a key tricyclic intermediate in the synthesis of roseophilin using RCM, where initial attempts[23] to build a macrocycle around a fused [5.5] ring system proved challenging, but reversing the order of ring construction [i.e. initial construction of a macrocycle, followed by creation of the smaller rings[24]] provided an easier route. (More recently, another synthesis succeeded[25] in preparing the macrocycle around the [5.5] ring system in a very efficient manner.)

To demonstrate that route (b) could indeed lead through to the desired muscothiazoles **2b**,**c**, macrocycle **13b** was converted to thiazole **7b** in 88% yield, while **13c** afforded **7c** in a similar yield (86%). Finally, palladium-catalyzed hydrogenation of compounds **7b** and **7c** respectively afforded

(12) (a) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137. (b) Edwards, S. D.; Lewis, T.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, *40*, 4267. (c) Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 725. (d) Bourgeois, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *Synthesis* **2000**, 869.

(13) For formation of "deletion" products, see: (a) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123. (b) Joe, D.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635.

(14) (a) Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J Organomet. Chem.* **2002**, *643*−*644*, 247. (b) For formation of another "deletion" product, see: Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

(15) We examined the possibility that complexation of the thiazole to the metathesis catalyst was impeding the reaction (*J. Org. Chem.* **1999**, *64*, 8275) by repeating the experiment in the presence of 1 equiv of *p*-toluenesulfonic acid. No difference was observed. The later successful cyclizations of the monomethyl analogues may be taken as support that complexation was not the cause of the problem.

(16) (a) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108. (b) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. (c) Fürstner, A.; Langeman, K. *J. Org. Chem.* **1996**, *61*, 8746. (d) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127. (e) Delgado, M.; Martin, J. D. *Tetrahedron Lett.* **1997**, *38*, 6299.

(17) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548.

(18) Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919.

(19) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291.

(20) That was a complex structure, where one ethyl-substituted stereoisomer cyclized well and the other did not; the origin of the effect was not so transparent as in our current simpler molecules.

(21) For a clear effect on product stereochemistry, see: Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942.

(22) Substrates **12a**−**d** reacted rapidly (average reaction time 3.5 h).

(23) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601.

(24) (a) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361. (b) Harrington, P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649.

(25) Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **2000**, *2*, 1157.

the desired target muscothiazoles **2b** and **2c** (100%) (not shown in Scheme 2). As expected, these compounds have a pleasant musk odor.

Our study shows that a single methyl substitution[26] on a linear chain containing the reactive centers significantly enhances the efficiency of formation of the macrocyclic product.

We propose that many RCM cyclizations of carbon substrates that are unsuccessful with a parent substrate could be achieved in good yield by introducing an appropriately placed temporary substituent, e.g. a chlorine atom, onto a reacting chain. This, together with calculations on the energetics of this process, is currently under investigation in our laboratories.

(26) For a recent discussion of the effect of *gem*-disubstitutions on reaction rates, see: Jung, M. E. *Synlett* **1999**, S1, 843 and references therein.

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Supporting Information Available: Procedures and characterizations for compounds **5a**−**d**, **7a**−**d**, **12a**−**d**, **13a**−**d,** and **2b,c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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