Conformationally Unbiased Macrocyclization Reactions by Ring Closing Metathesis

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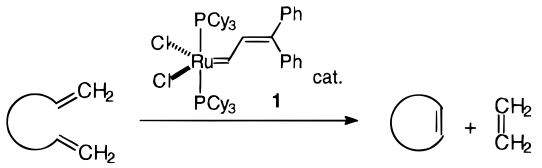
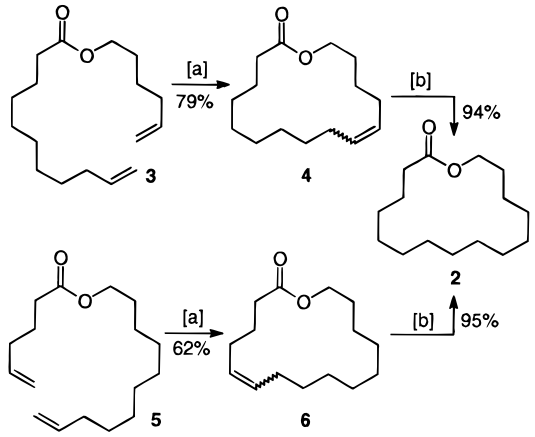
The discovery of well-defined single component metathesis catalysts has had a great impact on organic synthesis and on polymer chemistry.[1] Among them, the ruthenium carbene **1** is particularly noteworthy.[2,3] The well-balanced electronic and coordinative unsaturation of its Ru^{2+} center accounts for its high performance as well as for the remarkable tolerance toward an array of functional groups. Both features are evident from many applications of this catalyst to the formation of fairly complex 5-, 6, and 7-membered carbo- and heterocycles by ring-closing metathesis (RCM) of suitable diolefin precursors (Scheme 1).[4] The formation of medium or large ring systems, however, is yet largely unexplored and impaired by the assumption that only conformationally predisposed dienes are suitable starting materials.[5,6] The syntheses of natural odoriferous macrolides reported below prove that this is not the case since *substrates devoid of any conformational contraints can be efficiently cyclized by RCM to macrocyclic products*. Even more surprisingly, they highlight the notion that RCM is amongst the most straightforward entries into large ring systems and favorably compares to all current alternatives.[7]

Scheme 1



Scheme 2[a]



[a] Key: (a) **1** (4 mol %), CH_2Cl_2; (b) H_2 (1 atm), Pd/C.

On principle, olefin metathesis is a reversible process and therefore under thermodynamic control.[1] As RCM generates two molecules from one with evaporative loss of, *e.g.*, ethene as the byproduct (Scheme 1), the gain in entropy should provide sufficient driving force whenever ΔH is small. This is expected to be the case for the formation of a highly flexible macrocycle from an equally flexible acyclic diene precursor. Exaltolide (**2**), a valuable musk-odored olfactory ingredient of *Archangelica officinalis*,[8] was chosen as target in order to test this hypothesis (Scheme 2).

Acylation of 1-hex-5-enol with 10-undecenoyl chloride or of 10-undecen-1-ol with 5-hexenoic acid gave dienes **3** and **5**, respectively. Slow addition of a CH_2Cl_2 solution of these compounds to a solution of the Grubbs carbene **1** (4 mol %) in the same solvent at ambient temperature led to the corresponding 16-membered lactones **4** (*Z*:*E* = 54:46) and **6** (*Z*:*E* = 23:77) in excellent yields. Hydrogenation of these compounds afforded **2** almost quantitatively. Our synthesis of this valuable perfumery ingredient requires only three steps from commercially available starting materials and is therefore significantly more efficient than previous approaches.[8]

Even much larger rings can be readily accessed by RCM. This is evident from the synthesis of 20-eicosanolide **7**, a major component in the secretion of the abdominal Dufour gland of solitary bees of the genera *Colletes* and *Halictus*.[9] This product is easily prepared by acylation of 10-undecen-1-ol with 10-undecenoyl chlo-

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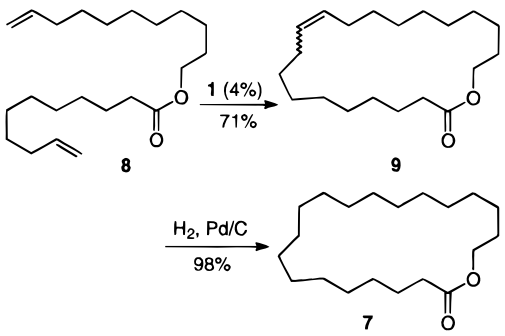
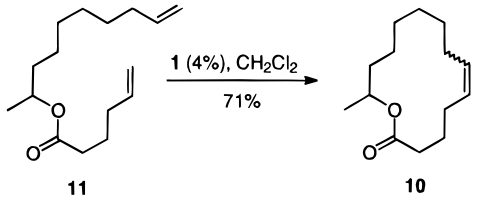
Scheme 3



Scheme 4



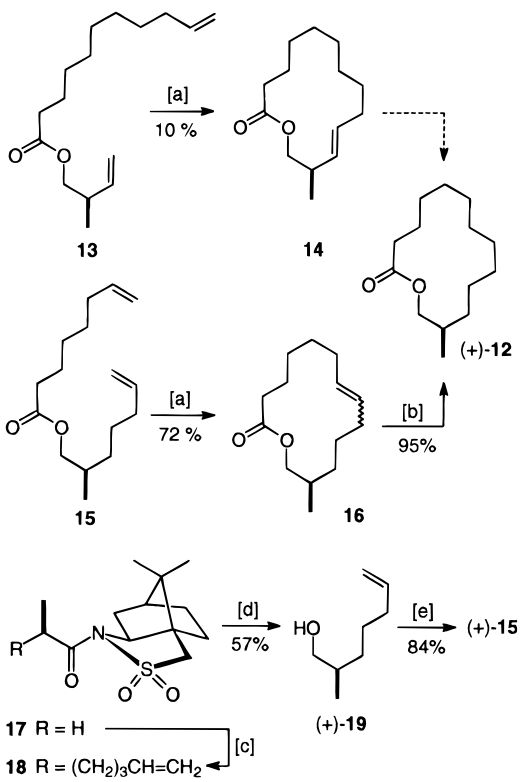
ride (95%), followed by efficient RCM of the resulting 1,ω-diene **8** as described above and final hydrogenation of the resulting unsaturated macrocycle **9** (*Z*:*E* = 55:45) (Scheme 3). Thus, a sequence of only three steps converts well accessible substrates into the 21-membered lactone **7** in 66% *overall* yield. This approach is distinguished by its unparallelled straightness, efficiency and "atom economy"[10] from conceivable alternatives.

The 14-membered macrolide **10**, the (5*Z*,13*S*)-enantiomer of which is a synergist of the aggregation pheromone of the flat grain beetle *Cryptoletes pusillus*,[11] is also readily assembled. DCC-mediated esterification of 9-decen-2-ol with 5-hexenoic acid (88%) followed by RCM of the resulting diene **11** with 4 mol % of the Ru-carbene **1** afforded the desired product as a mixture of the geometrical isomers (*Z*:*E* = 69:31) (Scheme 4).

A final application of RCM to the synthesis of enantiomerically pure (*12R*)-(+)-12-methyl-13-tridecanolide (**12**), a minor musk-odored component of *Angelica* root oil,[12] may help to define the essential parameters for productive metathetic ring closure and to assess the scope of RCM in a more realistic way (Scheme 5).

Acylation of commercially available 2-methyl-3-buten-1-ol with 10-undecenoyl chloride gave diene (±)-**13** in 68% yield. Treatment of this substrate with catalytic amounts of **1** under standard conditions, however, led to the desired macrocycle **14** in disappointingly low yield (10%, GC yield 24%, (*E*)-isomer only). In contrast, RCM of derivative (±)-**15** proceeded smoothly, affording the 14-membered lactone (±)-**16** in 72% isolated yield (*E*:*Z* = 96:4), which was hydrogenated to racemic **12**. This latter approach is easily adapted to the synthesis of enantiomerically pure (+)-**12**. Alkylation of *N*-propionylbornane-10,2-sultam (**17**) with 1-iodo-4-pentene according to

Scheme 5[a]



[a] Key: (a) **1** (4 mol %), CH_2Cl_2; (b) H_2 (1 atm), Pd/C; (c) $NaN(SiMe_3)_2$, 5-iodo-1-pentene, −78 °C → rt, THF/HMPA, overnight; (d) $LiAlH_4$, THF, 57% over steps c and d; (e) 7-octenoyl chloride, DMAP, CH_2Cl_2.

Oppolzer's protocol,[13] followed by reduction of the resulting amide with $LiAlH_4$, gave alcohol (+)-**19** (ee > 99%, $[\alpha]^{23}_D = +10.4$ (*c* 14.0, CH_2Cl_2)). Subjecting this material to the sequence described above cleanly led to the optically active olfactory product (+)-**12** (ee > 99%; $[\alpha]^{25}_D = +14.54$ (*c* 4.25, CH_2Cl_2) (lit.[12d] $[\alpha]^{25}_D = +14.7$ (*c* 1.4))). This synthesis clearly surpasses previous ones in terms of accessibility of the substrates, number of steps, flexibility, atom economy, optical purity, and overall yield.

Since the approaches to lactone **12** displayed in Scheme 5 differ only in the *site of ring closure* it is evident that this parameter rather than the ring size formed is *pivotal for productive RCM*. The poor reactivity of **13** may arise from the steric effect of the adjacent methyl substituent and/or from sequestering the catalyst in form of unproductive chelate complexes due to the coordination of the ester group onto the proximate Ru carbene intermediate.[14] We are presently probing this aspect in more detail.

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Supporting Information Available: Representative procedures and the analytical data of all products (7 pages).

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