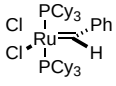
Synthesis of Medium-Sized Rings by the Ring-Closing Metathesis Reaction

Martin E. Maier*

The construction of rings represents a central theme in natural product synthesis.[1] Among the various available options, such as cycloaddition reactions, ring transformations, and cyclization reactions, the latter are probably the most commonly used because of the number of possible initiators and terminators. However, not every ring size is accessible with the same ease. Because of enthalpic (increasing strain in the transition state) and entropic influences (probability of the chain ends meeting), medium-sized rings are the most difficult to prepare. Among the many cyclization reactions, the olefin metathesis reaction (ring-closing olefin metathesis, RCM) has gained enormous popularity in recent years.[2–7] In this reaction, nonconjugated dienes are converted to cyclic alkene structures in the presence of a metal carbene complex. Catalysts developed by Grubbs and Schrock are commonly used for that purpose due to their high reactivity.

The Grubbs catalyst **1** (Cy = cyclohexyl) is very easy to prepare, commercially available, and air stable.[8] On the other hand, the preparation of the Schrock catalyst **2** is a more elaborate undertaking,[9] Nonetheless, **2** is also commercially available. Recently, novel air- and water-tolerant ruthenium complexes like **3** were introduced and shown to exhibit increased metathesis activity as compared to **1**.[10, 11] These complexes are even able to induce cyclization to tetrasubstituted cycloalkenes.



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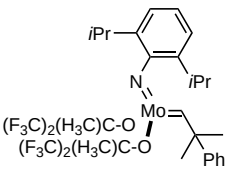

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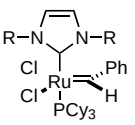


3

R = C_6H_2-2,4,6-$(CH_3)_3$

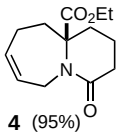
A great advantage of the RCM is the involvement of relatively stable double bonds. This facilitates synthesis and handling of the cyclization precursors. In light of this, it is no wonder that the McMurry cyclization[12, 13] of dialdehydes has some serious competition.

[*] Prof. Dr. M. E. Maier
Universität Tübingen
Institut für Organische Chemie
Auf der Morgenstelle 18, 72076 Tübingen (Germany)
Fax: (+49) 7071-29-5137
E-mail: martin.e.maier@uni-tuebingen.de

An elegant application of the RCM reaction has been the formation of the 16-membered macrocycle of the epothilones.[14–20] Other natural product syntheses in which the RCM reaction has been instrumental include those of roseophilin,[21–23] and manzamine-type alkaloids,[24] among others.[7] In additition, an RCM reaction was used in a total synthesis of the streptogramin antibiotic (−)-griseoviridin to combine a terminal 1,3-dienyl group and an alkenyl group to provide the macrocyclic ring with a 1,3-diene.[25]

In contrast, only recently were successful RCM reactions for medium-sized rings reported. In order to facilitate the desired cyclization, several features were installed in the substrate that provide some sort of conformational constraint. These constraints were achieved either by using preexisting rings (cyclic conformational constraints) or acyclic conformational constraints. In the following text, I will illustrate some of this work.

Attachment of olefinic side chains to lactams facilitates the RCM cyclization, as shown by several groups.[26] For example, seven- to nine-membered bicyclic lactams **4**–**6** were formed easily using the Grubbs catalyst **1** in dichloromethane at room temperature.[27] Similarly, macrocyclic rings could be annulated onto a β-lactam (**7**, **8**)[28] and onto a pyrrolidine ring system (**9**, **10**).[29] Compounds of this type are of interest as turn-inducing structures in small peptides.



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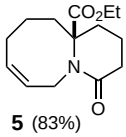

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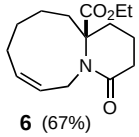

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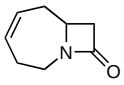

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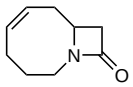

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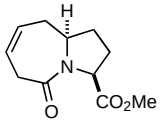

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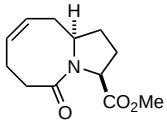

10 (35%, 54% recovered starting material)

In order to establish a seven-membered nitrogen heterocycle carrying a 1,2-amino alcohol by an RCM cyclization, the group of Cook et al. used an oxazoline ring as a constraint.[30] The substrate **11** was prepared from D-serine utilizing a

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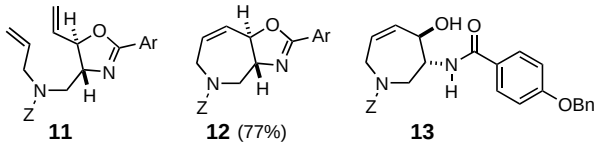
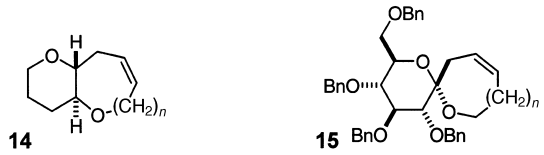
palladium-catalyzed equilibration of vinyloxazolines to control the stereochemistry of the vicinal amino alcohol. As deduced from force-field calculations, the torsional angle of the side chains in **11** is about 95°, which is easily accommodated by the bicyclic structure **12**. Accordingly, the alkene metathesis reaction with 10 mol% of the Grubbs catalyst in refluxing dichloromethane furnished the heterocycle **12** in 77% yield. Compound **12** was transformed into the hexahydroazepine **13**, which is an intermediate in the synthesis of balanol, a potent protein kinase C inhibitor.



The RCM approach turned out to be very useful for the synthesis of medium-sized oxacycles. Such cyclic ethers occur in a number of biologically active natural products such as the brevetoxins. If the olefinic side chains are positioned on the ring vicinal to each other, the cyclizations are very facile. Examples include the *trans*-fused polyether systems **14** (Figure 1).[31, 32] Only for the nine-membered ring does a decreased yield point to some steric hindrance in the transition state. Further, the oxygen atoms seem not to interfere with the catalytic cycle. Macrocyclic spiro rings of type **15** could be additionally attached to a sugar derivative.[33]



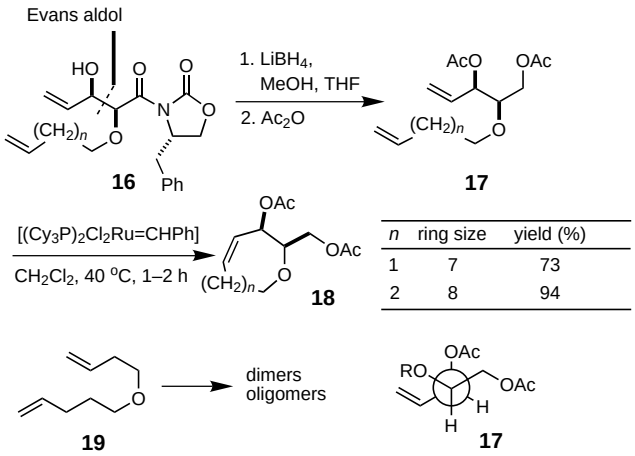
n	ring size	yield (%)
1	7	95
2	8	95
3	9	40

n	ring size	yield (%)
1	7	95
2	8	90

Figure 1. Grubbs catalyst **1** in the preparation of oxacyclene. Bn = benzyl.

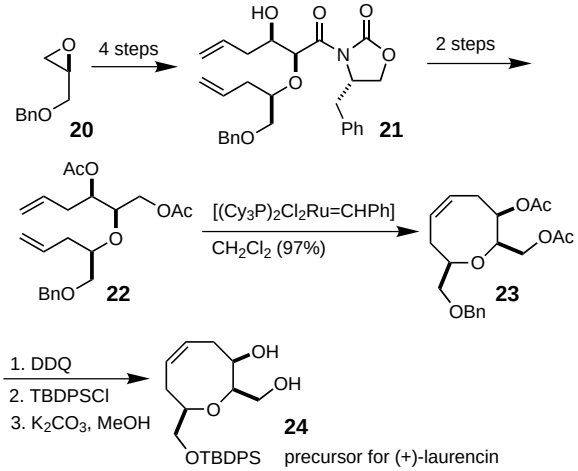
Besides using a ring in order to limit the conformational freedom of a chain, appropriately positioning substituents on the chain carrying the two olefinic groups can boost the macrocyclization. The group of Crimmins reported on the use of the *gauche* effect of 1,2-dioxygen substituents to facilitate the ring closure (Scheme 1).[34] They also demonstrated the power of the RCM approach by establishing some very simple routes to chiral ether cyclization substrates. For example, an Evans aldol reaction of glycolate imides with acrolein led to the α,β-dihydroxy acid derivative **16**. Subsequent reduction and acetylation provided the dienes **17**, which could in turn be easily cyclized with excellent yields by the ruthenium carbene complex **1**. Since the ether **19** gave only dimers and oligomers, it was suggested that the vicinal stereo centers in **17** induce conformations where the olefinic chains are positioned *gauche* (see the Newman projection of **17**).[34, 35]

This concept was applied to the synthesis of a key precursor of the natural product (+)-laurencin (Scheme 2). One stereo-



n	ring size	yield (%)
1	7	73
2	8	94

Scheme 1. Use of the *gauche* effect of 1,2-dioxygen substituents to enhance the ring-closing reaction. Ac = acetyl.



Scheme 2. Synthesis of the laurencin precursor **24**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TBDPS = *tert*-butyldiphenylsilyl.

center was fashioned from (*R*)-benzyl glycidyl ether **20**, whereas the other two came from an aldol reaction. As in the model studies, the eight-membered ring **23** formed with an excellent yield.

Subsequently, the same group published a more direct synthesis of (+)-laurencin, in which the ethyl side chain was included early in the synthesis (Scheme 3).[36] Instead of aldol reactions, asymmetric alkylation reactions were used to set two of the stereocenters. Thus, the diol **25** was prepared by allylation of a benzyl glycolate imide followed by a chelation-controlled ethylation of the derived aldehyde. Another allylation of **26** provided the diene **27** that cyclized to the oxocene **28**. Further steps were needed to change the protecting group, generate the aldehyde **29**, and to elongate the side chain. The addition of the chlorotitanium enolate of (*S*)-(+)-3-acetyl-4-isobutyl-2-thiazolidinone gave a diastereomeric mixture of alcohols **30**. Finally, a Wittig elongation led to the natural product **32**.

A number of natural products contain medium-sized lactone rings. Therefore, synthetic routes to these compounds

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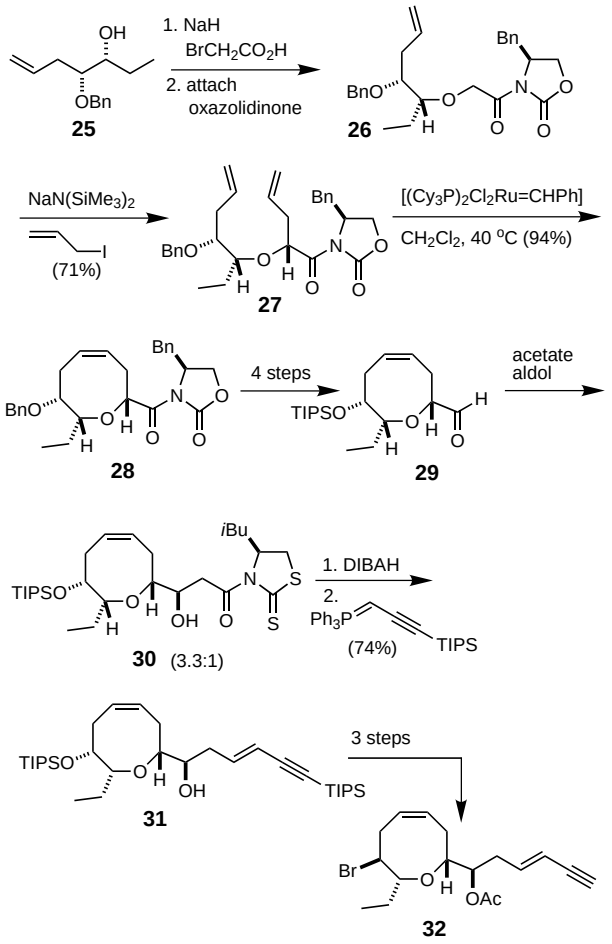
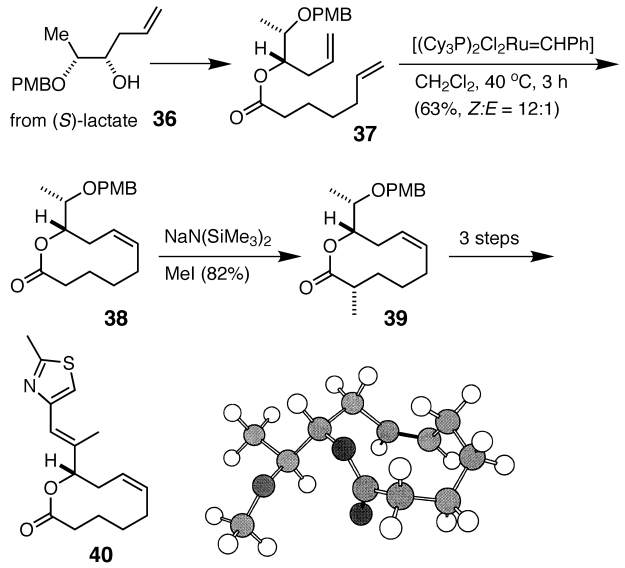


Scheme 3. Synthesis of laurencin **32**. TIPS = triisopropylsilyl; DIBAH = diisobutylaluminum hydride.

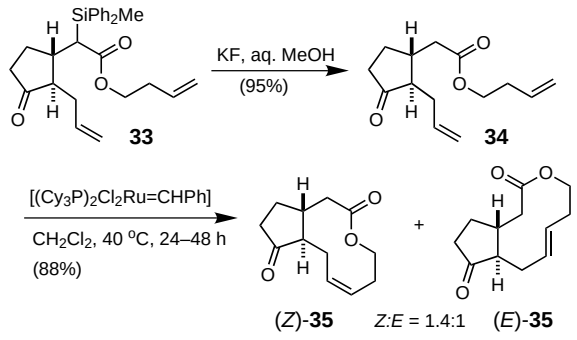
are highly desirable. Usually, macrolactonization reactions under highly dilute conditions or Baeyer–Villiger ring expansions are used to reach these targets. The group of Fürstner reported on the first successful synthesis of a ten-membered lactone by olefin metathesis (Scheme 4).[37] Starting from cyclopentenone, a Michael addition–allylation sequence provided the cyclopentanone **33**. The silicon substituent makes the enolate a softer base and favors the 1,4-addition. The cyclization was effected by slowly combining solutions of **34** and **1** (10 mol%) and refluxing the mixture. While the cyclization was possible, the reaction led to double bond isomers in a moderate ratio. Compound (*Z*)-**35** is a component of the essential oil from jasmine. Most likely the constraint imposed by the five-membered ring favors cyclization over dimerization.

The Kalesse group subsequently described the synthesis of the ten-membered lactone **38** by an RCM reaction (Scheme 5).[38] It is, however, not clear what is the role of the substituent during the cyclization. In any case, the stereochemical information of **38** was used to establish another stereocenter by a stereoselective alkylation of the medium-sized ring enolate. The cyclization also works with an acyclic precursor of **40**.[39] The model illustrates the calculated conformation of **38** and explains the stereochemical situation for the alkylation of **38** to **39**.

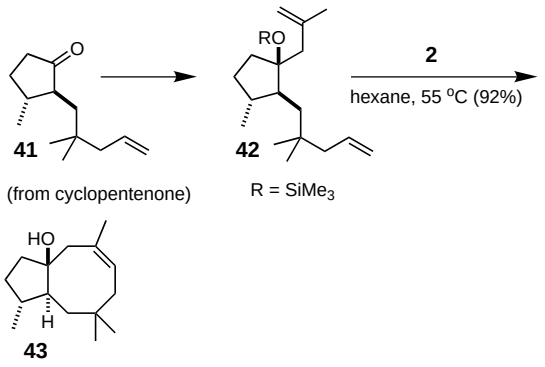


Scheme 5. Olefin metathesis for the synthesis of unsaturated ten-membered lactone rings after Kalesse et al. PMB = *p*-methoxybenzyl. The model shows the calculated conformation of **38**.

In principle, the same concept of conformational constraints can be used as a driving force in the preparation of medium-sized carbocycles (Scheme 6). An illustrative case is the synthesis of dactylol **43** using an RCM cyclization as a key step.[40] The reaction catalyst was the Schrock molybdenum carbene complex **2** in hexane. The hydroxyl group of **42**



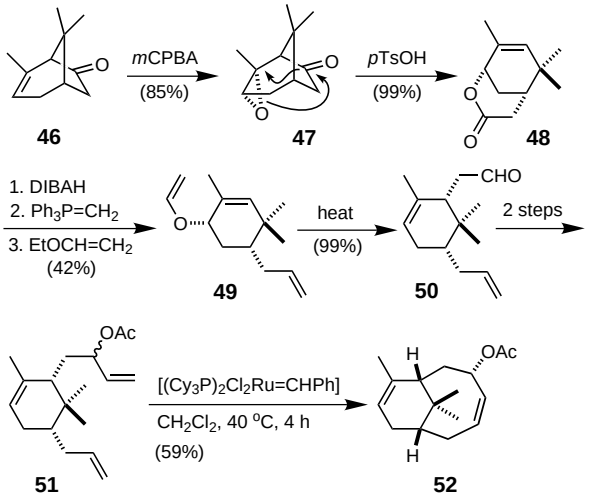
Scheme 4. Olefin metathesis for the synthesis of unsaturated ten-membered lactone rings after Fürstner et al.



Scheme 6. Conformational constraints as a controlling force for the cyclization of medium-sized carbocycles.

needed to be protected as a silyl ether, otherwise the cyclization failed completely. Another instance of this kind is the annulation of eight-membered rings onto a sugar template, although moderate yields were reported for compounds **44** and **45**.[41]

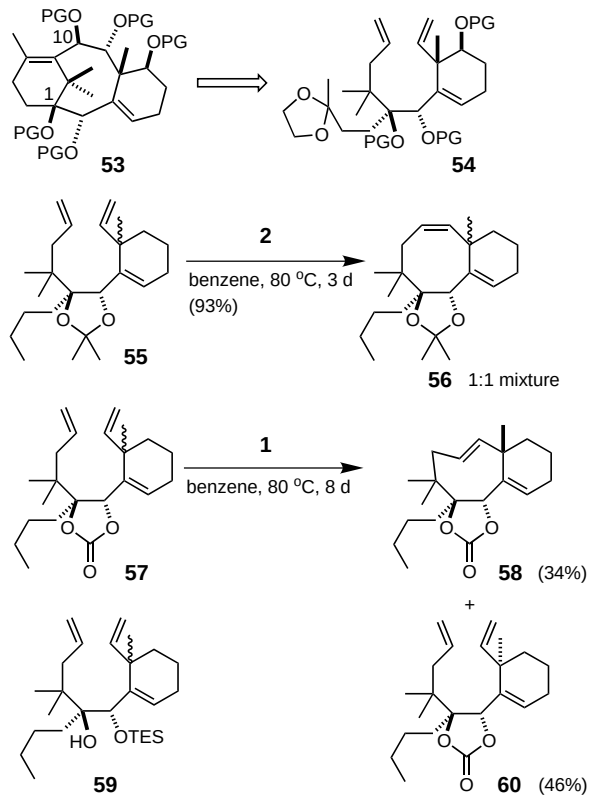
Clearly, bridged-ring systems, such as the one found in taxol, represent a formidable challenge for synthesis. Some of the difficulties in preparing the taxol skeleton are due to the geminal dimethyl groups. Nevertheless, an A,B-ring fragment could be synthesized by Blechert et al. by invoking an RCM reaction (Scheme 7).[42] Starting from (−)-β-pinene, an iron-catalyzed CO insertion led to the ketone **46** and an isomeric



Scheme 7. Synthesis of a taxol A,B ring fragment by the RCM reaction after Blechert et al. *m*CPBA = 3-chloroperoxybenzoic acid; pTs = *p*-sulfonyl toluene.

ketone (not shown). Both compounds could be ultimately converted to the bridged lactone **48**: Epoxidation of **46** gave **47**, which rearranged in the presence of catalytic amounts of *p*TsOH in dichloromethane to the bridged lactone **47**. The *cis*-configuration of **48** was transformed to the aldehyde **50** through a Claisen rearrangement. Then **50** was converted to the cyclization substrate **51**. It was discovered that only one of the vinyl acetate diastereomers cyclized in the presence of the Grubbs catalyst. It is probable that the conformation required for the cyclization is unfavored for the β-acetate by a strong steric interaction with the geminal dimethyl groups of the cyclohexene.

The importance of conformational control on the outcome of RCM reactions was nicely demonstrated in a recent publication by Prunet et al.[43] This group reported on the synthesis of the B,C ring systems of taxol by forming the central eight-membered ring. The overall synthetic plan is illustrated in Scheme 8. The eight-membered ring is envisioned to originate from an RCM reaction and a final intramolecular aldol condensation should complete the synthesis of the core structure **53**. During the cyclization to form the cyclooctene, not only a substantial enthalpic barrier must be overcome but the cyclization might also be impaired by steric hindrance from the olefin which is in a neopentilic position. In fact, the taxol model system **59**, when treated



Scheme 8. Synthesis of the taxol B,C ring fragments after Prunet et al. PG = protective group; TES = triethylsilyl.

with **1** (0.02 M in benzene, 80 °C, 8 d), gave only a low yield of cyclized products. However, a cyclic protecting group as in **55** brought about a positive effect. While **1** failed to produce macrocyclic products, the Schrock catalyst **2** delivered the cyclooctene **56** (as a separable mixture of diastereomers) in high yield. Most likely, the conformational constraint places the two double bonds at a suitable distance for the metathesis reaction. Based on these results, one would expect a similar result using the substrate **57**, in which a cyclic carbonate functions as a constraint. Surprisingly, the RCM cyclization gave the *trans*-cyclooctene **58**, whose structure was confirmed by X-ray analysis. This compound was formed only from one of the two isomers; the other diastereomer **57** was recovered unchanged. This result is more or less independent of the catalyst used (10 mol% **1**, benzene, 80 °C, 8 days; 10 mol% **2**, benzene, 80 °C, 3 days). Since it is generally believed that the metathesis occurs under thermodynamic control, this result is quite unusual.

In summary, the examples mentioned above illustrate the broad applicability of the RCM cyclization for the synthesis of medium-sized carbocycles and heterocycles. It is clear that this reaction will become—or even already is—a classical transformation in organic chemistry. For medium-sized rings, it is beneficial to use conformational constraints such as rings or stereoelectronic effects.

[1] K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. Baran, *Angew. Chem.* **2000**, *112*, 46–126; *Angew. Chem. Int. Ed.* **2000**, *39*, 44–122.
[2] R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446–452.

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[3] M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124 – 2145; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036 – 2055.
[4] A. Fürstner, *Top. Catal.* **1997**, *4*, 285 – 299.
[5] S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371 – 388.
[6] R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413 – 4450.
[7] A. Fürstner, *Synlett* **1999**, 1523 – 1533.
[8] E. L. Dias, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1997**, *119*, 3887 – 3897.
[9] R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875 – 3886.
[10] M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 2247 – 2250.
[11] L. Ackermann, A. Fürstner, T. Weskamp, F. J. Kohl, W. A. Herrmann, *Tetrahedron Lett.* **1999**, *40*, 4787 – 4790.
[12] S. H. Pine, *Org. React.* **1993**, *43*, 1 – 91.
[13] A. Fürstner, B. Bogdanović, *Angew. Chem.* **1996**, *108*, 2582 – 2609; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2442 – 2469.
[14] P. Bertinato, E. J. Sorensen, D. Meng, S. J. Danishefsky, *J. Org. Chem.* **1996**, *61*, 8000 – 8001.
[15] K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, Z. Yang, *Angew. Chem.* **1996**, *108*, 2554 – 2556; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2399 – 2401.
[16] D. Meng, D.-S. Su, A. Balog, P. Bertinato, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. Horwitz, *J. Am. Chem. Soc.* **1997**, *119*, 2733 – 2734.
[17] K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang, J. I. Trujillo, *J. Am. Chem. Soc.* **1997**, *119*, 7960 – 7973.
[18] Z. Yang, Y. He, D. Vourloumis, H. Vallberg, K. C. Nicolaou, *Angew. Chem.* **1997**, *109*, 170 – 172; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 166 – 168.
[19] K. C. Nicolaou, D. Vourloumis, T. Li, J. Pastor, N. Winssinger, Y. He, S. Ninkovic, F. Sarabia, H. Vallberg, F. Roschangar, P. N. King, M. R. V. Finlay, P. Giannakakou, P. Verdier-Pinard, E. Hamel, *Angew. Chem.* **1997**, *109*, 2181 – 2187; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2097 – 2102.
[20] D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm, M. Cordes, *Angew. Chem.* **1997**, *109*, 543 – 544; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 523 – 524.
[21] S. H. Kim, I. Figueroa, P. L. Fuchs, *Tetrahedron Lett.* **1997**, *38*, 2601 – 2604.
[22] A. Fürstner, T. Gastner, H. Weintritt, *J. Org. Chem.* **1999**, *64*, 2361 – 2366.
[23] P. E. Harrington, M. A. Tius, *Org. Lett.* **1999**, *1*, 649 – 651.
[24] S. F. Martin, J. M. Humphrey, A. Ali, M. C. Hillier, *J. Am. Chem. Soc.* **1999**, *121*, 866 – 867.
[25] C. A. Dvorak, W. D. Schmitz, D. J. Poon, D. C. Pryde, J. P. Lawson, R. A. Amos, A. I. Meyers, *Angew. Chem.* **2000**, *112*; *Angew. Chem. Int. Ed.* **2000**, *29*, in press.
[26] S. J. Miller, S.-H. Kim, Z.-R. Chen, R. H. Grubbs, *J. Am. Chem. Soc.* **1995**, *117*, 2108 – 2109.
[27] N. Diedrichs, B. Westermann, *Synlett* **1999**, 1127 – 1129.
[28] C. A. Tarling, A. B. Holmes, R. E. Markwell, N. D. Pearson, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1695 – 1701.
[29] C. E. Grossmith, F. Senia, J. Wagner, *Synlett* **1999**, 1660 – 1662.
[30] G. R. Cook, P. S. Shanker, S. L. Peterson, *Org. Lett.* **1999**, *1*, 615 – 617.
[31] M. Delgado, J. D. Martín, *J. Org. Chem.* **1999**, *64*, 4798 – 4816.
[32] H. Oguri, S.-Y. Sasaki, T. Oishi, M. Hirama, *Tetrahedron Lett.* **1999**, *40*, 5405 – 5408.
[33] P. A. V. van Hooft, M. A. Leeuwenburgh, H. S. Overkleeft, G. A. van der Marel, C. A. A. van Boeckel, J. H. van Boom, *Tetrahedron Lett.* **1998**, *39*, 6061 – 6064.
[34] M. T. Crimmins, A. L. Choy, *J. Am. Chem. Soc.* **1999**, *121*, 5653 – 5660.
[35] S. D. Edwards, T. Lewis, R. J. K. Taylor, *Tetrahedron Lett.* **1999**, *40*, 4267 – 4270.
[36] M. T. Crimmins, K. A. Emmitte, *Org. Lett.* **1999**, *1*, 2029 – 2032.
[37] A. Fürstner, T. Müller, *Synlett* **1997**, 1010 – 1012.
[38] K. Gerlach, M. Quitschalle, M. Kalesse, *Tetrahedron Lett.* **1999**, *40*, 3553 – 3556.
[39] M. Quitschalle, M. Kalesse, *Tetrahedron Lett.* **1999**, *40*, 7765 – 7768.
[40] A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 8746 – 8749.
[41] D. J. Holt, W. D. Barker, P. R. Jenkins, D. L. Davies, S. Garratt, J. Fawcett, D. R. Russell, S. Ghosh, *Angew. Chem.* **1998**, *110*, 3486 – 3488; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3298 – 3300.
[42] M. Wenz, D. Grossbach, M. Beitzel, S. Blechert, *Synthesis* **1999**, 607 – 614.
[43] D. Bourgeois, A. Pancrazi, L. Ricard, J. Prunet, *Angew. Chem.* **2000**, *112*, 741 – 744; *Angew. Chem. Int. Ed.* **2000**, *39*, 726 – 728.

New Sulfur- and Selenium-Based Traceless Linkers—More than just Linkers?

Florencio Zaragoza*

Linkers that enable the release of unfunctionalized hydrocarbons (alkanes, alkenes, arenes) from insoluble supports are attracting considerable interest.[1] Such "traceless" linkers can give access to compound libraries devoid of a common functional group that was required for covalent attachment of the intermediates to the support. The production of highly diverse libraries by solid-phase synthesis should, therefore, be possible with such linkers. Herein some new strategies for traceless linking based on the cleavage of C-S or C-Se bonds are presented.

[*] Dr. F. Zaragoza
Novo Nordisk A/S
Novo Nordisk Park
2760 Måløv (Denmark)
Fax: (+45) 4466-3450
E-mail: flo@novo.dk

Sulfur-Based Linkers

The carbon – sulfur bond in thioethers can be cleaved by photolysis[2] or with reducing agents such as Raney nickel or tin hydrides.[3] These cleavage conditions are not easily adapted to parallel synthesis, and only a few examples of thioether-based traceless linking have been reported.[2, 3] Sulfones, available by oxidation of thioethers with *m*-chloroperbenzoic acid (MCPBA), are generally too stable to undergo homolytic or heterolytic C–S bond cleavage under suitably mild conditions to yield unfunctionalized hydrocarbons.[4] More reactive than thioethers or sulfones, however, are trialkylsulfonium salts, which can be prepared on cross-linked polystyrene by the S-alkylation of thioethers with trialkyloxonium salts. Polystyrene-bound trialkylsulfonium salts have recently been introduced by Wagner and Mioskowski et al.[5] as new traceless linkers for the preparation of

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