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A Ring-Rearrangement Metathesis Approach toward the Synthesis of Cyclopenta- and Cyclohexa[*c*]indene Systems

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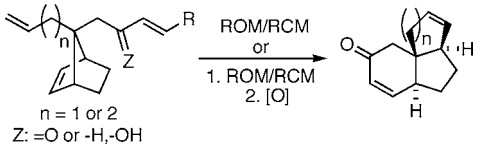
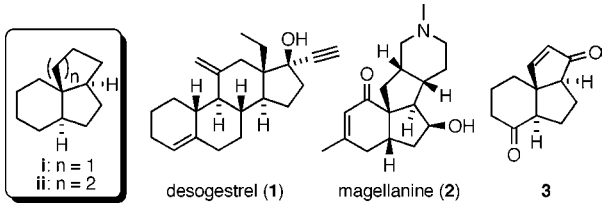
ABSTRACT



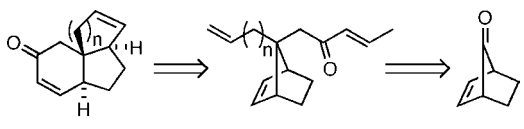
A highly efficient synthesis of angularly fused tricyclic enones, cyclopenta- and cyclohexa[*c*]indene skeletons, has been achieved by the tether-directed ring-rearrangement metathesis sequence starting with readily accessible norbornene derivatives bearing allyl and homoallyl groups at the bridging carbon.

The ubiquitous presence of nonlinear tricyclic cyclopenta- (**i**) and cyclohexa[*c*]indene (**ii**) skeletons and their equivalents in numerous complex natural products and pharmacologically significant molecules has stimulated considerable interest in the efficient construction of such systems.[1] In conjunction with our program directed at the synthesis of the oral contraceptive desogestrel (**1**)[2] and the alkaloid magellanine (**2**),[3] we had an opportunity to explore a new approach toward these angularly fused tricyclic skeletons. It should also be noted that the tricyclic ketone **3**, prepared by chemical degradation of vitamin D_2 followed by further functional group manipulations, has recently been used in the synthesis of side-chain-locked vitamin D analogues.[4]



A general approach toward these skeletons (see Scheme 1) is predicated upon using the tethered-alkene-directed ring-

Scheme 1. Retrosynthetic Analysis of Tricyclic Compounds **4** (n = 1 or 2)



(1) See, e.g.: (a) Tinao-Wooldridge, L. V.; Moeller, K. D.; Hidson, C. M. *J. Org. Chem.* **1994**, *59*, 2381−2389. (b) Kocovsky, P.; Dunn, V.; Gogoll, A.; Langer, V. *J. Org. Chem.* **1999**, *64*, 101−119 and references therein.

(2) Review: Teutsch, G.; Philibert, D. *Hum. Reprod.* **1994**, *9*, 12−31. For synthesis, see: (a) van den Broek, A. J.; van Bokhoven, C.; Hobbelen, P. M. J.; Leemhuis, J. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 35−39. (b) van den Heuvel, M. J.; van Bokhoven, C. W.; de Jongh, H. P.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 331−334. (c) Corey, E. J.; Huang, A. X. *J. Am. Chem. Soc.* **1999**, *121*, 710−714. (d) Hu, Q.-Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984−5986.

(3) For the synthesis of magellanine alkaloids, see: (a) Hirst, G. C.; Johnson, T. O.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992−2993. (b) Paquette, L. A.; Friedrich, D.; Pinard, E.; Williams, J. P.; St. Laurent, D. R.; Roden, B. A. *J. Am. Chem. Soc.* **1993**, *115*, 4377−4378. (c) Williams, J. P.; St. Laurent, D. R.; Friedrich, D.; Pinard, E.; Roden, B. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 4689−4696. (d) Yen, C.-F.; Liao, C.-C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4090−4093. (e) Ishizaki, M.; Niimi, Y.; Hoshino, O. *Tetrahedron Lett.* **2003**, *44*, 6029−6031.

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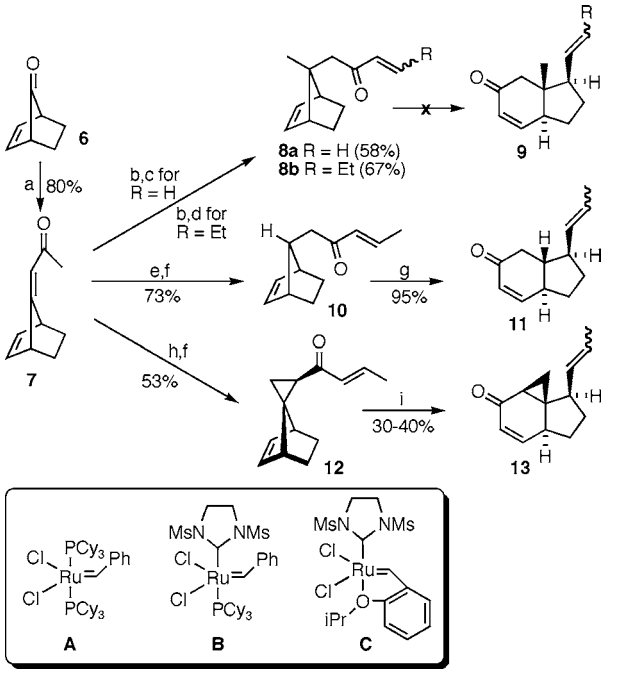
opening metathesis (ROM) of norbornene ring C═C bond followed by the ring-closing olefin metathesis (RCM)[5] involving the enone C═C double bond starting from the achiral bicyclic enone **5**. Enone **5** in turn was envisaged to be stereoselectively derived from readily accessible bicyclic ketone **6**[6] (see Scheme 1). Cyclopenta[*c*]indene derivative (**4**; $n = 1$) is foreseen as a pivotal intermediate toward desogestrel (**1**) and others.

Prior to the investigation of this directed metathesis rendition, a more direct ROM−RCM approach to access hydrindane compounds was first examined by supplanting an allylic or homoallylic group in enone **5** with an alkyl group (**8a** and **8b**, Scheme 2). Despite the extensive literature associated with the olefin metathesis of norbornenes,[5e,7,8] the steric hindrance of the juxtaposing *syn*-alkyl group at the norbornene bridge carbon was considered to be insurmountable for the sizable ruthenium-based olefin metathesis catalysts to overcome. Moreover, an issue that needed to be contemplated, in the event the catalyst's approach from the *exo*-face is inhibitive, concerned the possibility of the approach of the catalyst to the norbornene C═C bond from the *endo*-face.

In an effort to ascertain these facets of the reaction, enone **8** was prepared from **7**, which involved the initial stereoselective cuprate addition to the enone **7**. All attempts to achieve the ROM−RCM reaction from **8** with Grubbs's catalyst **A** or **B** resulted in the recovery of **8**. With the use of the more robust Hoveyda catalyst **C**, under forcing conditions, conversion to the dimer of **8** (as a single stereoisomer) involving the enone C═C bond was observed, suggesting that the presence of the *syn*-methyl group at the bridging carbon presents too much of a steric encumbrance for the metathesis reaction to take place with these ruthenium catalysts in this system. It is also interesting to note that the catalyst's approach from the *endo*-face of the norbornene

Scheme 2. ROC/RCM Reactions of Norbornene Derivatives[a]



[a] Reagents and conditions: (a) $Ph_3P{=}CHC(=O)CH_3$, benzene, reflux. (b) MeLi, CuCN, TMSCl, THF, −78 °C (95%). (c) (i) LDA, THF then TMSCl; (ii) $Me_2N^+{=}CH_2I^-$, CH_2Cl_2; (iii) MeI, THF; (iv) aq $NaHCO_3$, CH_2Cl_2 (61% yield for four steps).[9] (d) (i) LDA, THF; EtCHO; (ii) MsCl, pyridine; (iii) Et_3N, ether (70% yield for three steps). (e) $(Ph_3PCuH)_6$, benzene (95%).[10] (f) (i) LDA, THF; MeCHO; (ii) MsCl, pyridine; (iii) Et_3N, ether (77% yield for three steps). (g) catalyst **A** (1 mol %), CH_2Cl_2, room temperature. (h) $Me_3SO^+I^-$, NaH, DMSO (88%). (i) Catalyst **B** (10 mol %), CH_2Cl_2, room temperature.

apparently does not seem to be readily feasible with these ruthenium catalysts. To further gain insight into the steric requirement for the syn group attached to the bridging carbon, two other norbornene derivatives **10** and **12** were prepared. While enone **10** underwent a smooth ROM−RCM process to cleanly produce hydrindane **11** (as an *E*/*Z* mixture), the formation of the corresponding hydrindane **13** from cyclopropane enone **12** was observed to be much more slower and less efficient. These results further provided evidence that the metathesis reactions with the ruthenium catalysts could not effectively proceed when an alkyl group is placed on the bridging carbon syn to the norbornene C═C bond.[7,8] Additionally, ruthenium−methylidene complexes are known to be inefficient initiators for olefin metathesis reactions.[11] Therefore, the enone unit attached to the norbornene skeleton was designed to have a β-substituent. Thus, to minimize the formation of the methylidene complexes, a β-substituted enone was incorporated as an essential struc-

(4) Varela, C.; Nilsson, K.; Torneiro, M.; Mouriño, A. *Helv. Chim. Acta* **2002**, *85*, 3251−3261.

(5) (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vols. 1−3. For recent reviews, see: (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (d) Schrock, R. R. In *Carbene Chemistry*; Bertrand, G., Ed.; Marcel Dekker: New York, 2002; pp 205−230. (e) Grubbs, R. H.; Trnka, T. M.; Sanford, M. S. In *Current Methods in Inorganic Chemistry*; Kurokawa, H., Yamamoto, A., Eds.; Elsevier: Amsterdam, 2003; Vol. 3, pp 187−231. (f) Arjona, O.; Csáky, A. G.; Plumet, J. *Eur. J. Org. Chem.* **2003**, 611−622. (g) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923. (h) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (i) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8−23. (j) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (k) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239−2258.

(6) Gassman, P. G.; Pape, P. G. *J. Org. Chem.* **1964**, *29*, 160−163.

(7) (a) Feast, W. J.; Gibson, V. C.; Ivin, K. J.; Kenwright, A. M.; Khosravi, E. *J. Mol. Catal.* **1994**, *90*, 87−99. (b) North, M. In *Ring Opening Metathesis Polymerization and Related Chemistry*; Khosravi, E., Szymanska-Buzar, T., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2002; pp 157−166 and references cited therein.

(8) For some recent, select examples of the RCM reaction of norbornene compounds, see: (a) Schneider, M. F.; Lucas, N.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 257−259. (b) Stragies, R.; Blechert, S. *Synlett* **1998**, 169−170. (c) Hagiwara, H.; Katsumi, T.; Endou, S.; Hoshi, T.; Suzuki, T. *Tetrahedron* **2002**, *58*, 6651−6654. (d) Tsang, W. C. P.; Jernelius, J. A.; Cortez, G. A.; Weatherhead, G. S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 2591−2596.

(9) Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715−6717.

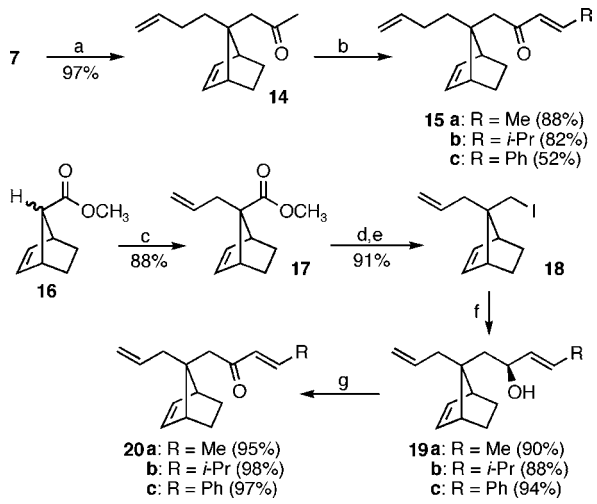
(10) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291−293.

(11) (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543−6554. (b) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414−7415.

tural feature in the system. Taken together, these considerations culminated in the formulation of the *syn*-alkenyl chain-directed ring-rearrangement metathesis approach shown in Scheme 1.[12,13]

The homoallyl-tethered enone **15** was readily accessible from norbornen-7-one (**6**) in four steps in 60% overall yield (Scheme 3). In contrast, allyl analogue **20** was not obtainable

Scheme 3. Synthesis of Alkene-Tethered Metathesis Precursors **15** and **20**

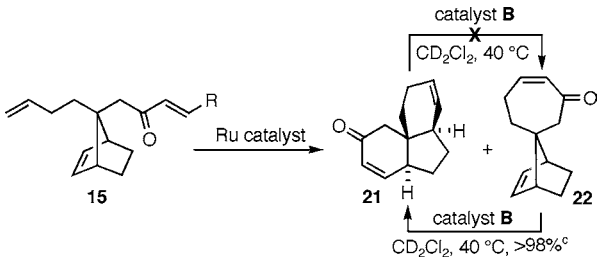


[a] Reagents and conditions: (a) $CH_2{=}CHCH_2CH_2MgBr$/CuBr·DMS, LiCl, TMSCl, THF, −78 °C. (b) (i) LDA, THF; R−CHO; (ii) MsCl, pyridine; (iii) Et_3N. (c) LDA, THF, −78 °C; allyl bromide. (d) $LiAlH_4$, THF (92%). (e) DCC·MeI (99%).[16] (f) *t*-BuLi, −78 °C, pentane/ether; *trans*-RCH=CHCHO. (g) TPAP, NMO, CH_2Cl_2, room temperature.

by a similar route, as conjugate allyl additions to enone **7** could not be realized. The problem was circumvented by the use of an epimeric mixture of ester **16**[14] which was in turn available in three steps in overall 61% yield from ketone **6** ((i) $Ph_3P^+CH_2OCH_3{\cdot}Cl^-$/KO^{t}Bu/ether, 0 °C; (ii) $HClO_4$, H_2O/ether; (iii) I_2/KOH, MeOH[15]). Allylation of **16** provided cleanly *syn*-allyl ester **17**, which was further transformed into trienone **20** in four steps (Scheme 3).

The results of the metathesis reactions of homoallyl-tethered trienone **15** using ruthenium-based reagents **A**−**C** are presented in Table 1. All of these catalysts were highly effective initiators of the metathesis reactions of **15**, thus making the metathesis approach a highly efficient route to

Table 1. Metathesis Reactions of Homoallyl-Tethered Trieneone **15**



15	catalyst[a]	solvent	temp	time	% yield	21:22
15a: R = Me	**B**	CH_2Cl_2	23 °C	14 h	>90[b]	22:78
15a: R = Me	**B**	benzene	23 °C	14 h	>90[b]	42:58
15a: R = Me	**A**	CH_2Cl_2	23 °C	14 h	>90[b]	>99:1
15a: R = Me	**A**	benzene	23 °C	24 h	62[b]	>98:2
15b: R = *i*-Pr	**B**	CD_2Cl_2	23 °C	3 h	>98[c]	>99:1
15c: R = Ph	**B**	CD_2Cl_2	23 °C	0.5 h	>98[c]	81:19
15c: R = Ph	**B**	CD_2Cl_2	40 °C	17 h	>98[c]	81:19
15c: R = Ph	**C**	CD_2Cl_2	23 °C	0.5 h	>98[c]	80:20
15c: R = Ph	**C**	CD_2Cl_2	40 °C	17 h	>98[c]	86:14
15c: R = Ph	**A**	CD_2Cl_2	23 °C	0.5 h	>98[c]	>99:1

[a] Performed with 5 mol % catalyst. [b] Isolated yield (as a mixture of **21** and **22**). [c] Yield estimated by ^{1}H NMR spectroscopy.

the tricyclic cyclohexa[*c*]indene system **21**.[8d] Interestingly, Grubbs's catalyst **A** was most selective in this reaction, as it quantitatively converted enone **15** (R = Me) into tricyclic enone **21** virtually without contamination by the spiro cycloheptenone **22** at 23 °C (14 h) in CH_2Cl_2. Cycloheptenone **22** could be isomerized to tricyclic enone **21** in the presence of catalyst **B**, but the reverse isomerization (i.e., **21** → **22**) was not observed, presumably manifesting the unfavorable thermodynamic energies of **22** due to the conjugated cycloheptenone[17] in addition to the severely strained norbornene structure.[18]

The metathesis reactions of allyl analogue **20** proved to be somewhat problematic. Table 2 describes the results based on the ^{1}H NMR analysis of the products from the metathesis reactions of trienone **20** under a variety of conditions. The metathesis reactions of **20** proceeded relatively quickly, particularly with catalyst **B**, with virtually no starting enone left. However, unlike the case of homoallyl analogue **15**, the formation of the spiro cyclohexenone product **24** persisted, presumably reflecting the relative stability of the six-membered conjugated ketone. The most favorable ratio of 2.4:1 between the two products **23** and **24** was observed when **20b** (R = *i*-Pr) was treated with catalyst **B** in CD_2Cl_2 at 23 °C for 1 h. Although this nominally corresponds to a 71% yield of the desired tricyclic enone **23**, the major difficulty encountered was that products **23** and **24** exhibited

(12) Randl, S.; Blechert, S. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, pp 151−175.

(13) A relayed RCM strategy is similar in its concept to what is described in this report but differs in that, in the former approach, the tether used does not end up in the product. See, for example: Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3601−3605 and references therein.

(14) (a) Bly, R. K.; Bly, R. S. *J. Org. Chem.* **1963**, *28*, 3165−3172. (b) Sauers, R. R.; Hawthorne, R. M. *J. Org. Chem.* **1964**, *29*, 21685−1687. (c) Bernaert, E.; Anteunis, M.; De Waele, R. *Bull. Soc. Chem. Belg.* **1973**, *82*, 795−802.

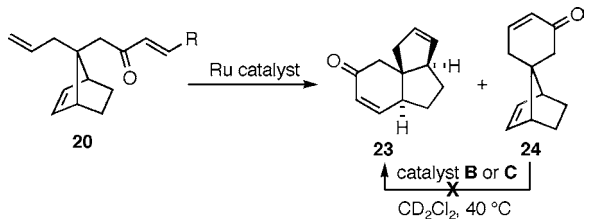
(15) Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329−4332.

(16) Scheffold, R.; Saladin, E. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 229−231.

(17) Heap, N.; Whitham, G. H. *J. Chem. Soc. B* **1966**, 164−170.

(18) Strain energy of norbornene is estimated to be 100 kJ/mol. (a) Lebedev, B.; Smirnova, N.; Kiparisova, Y.; Makovetsky, K. *Makromol. Chem.* **1992**, *193*, 1399−1411. (b) North, M. In *Advances in Strained and Interesting Organic Molecules*; Halton, B., Ed.; JAI Press: Stamford, CN, 2000; Vol. 8, pp 145−185.

Table 2. ^{1}H NMR Analysis of the Products from the Metathesis Reactions of Allyl-Tethered Trieneone **20**



20	catalyst[a]	solvent	temp	time	**20**:**23**:**24**
20a: R = Me	**A**	CD_2Cl_2	23 °C	0.5 h	7.9:0.1:1
20a: R = Me	**A**	CD_2Cl_2	40 °C	3 h	2.3:0.1:1
20a: R = Me	**B**	CD_2Cl_2	23 °C	0.5 h	1.1:1.1:1
20a: R = Me	**B**	CD_2Cl_2	40 °C	3 h	0:1:1
20a: R = Me	**B**	C_6D_6	23 °C	1 h	1.1:1:1.4
20a: R = Me	**B**	C_6D_6	45 °C	3 h	0:1:1.4
20b: R = *i*-Pr	**B**	CD_2Cl_2	23 °C	1 h	0:2.4:1
20b: R = *i*-Pr	**B**	CD_2Cl_2	23 °C	17 h	0:2.3:1
20b: R = *i*-Pr	**B**	CD_2Cl_2	40 °C	39 h	0:1.9:1
20c: R = Ph	**B**	CD_2Cl_2	23 °C	2 h	0:1.9:1
20c: R = Ph	**B**	C_6D_6	23 °C	2 h	0.1:1.9:1

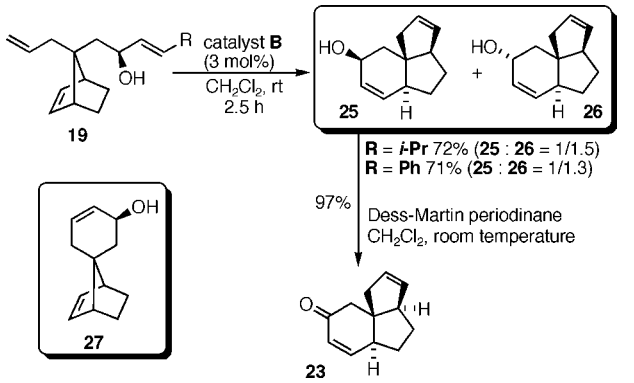
[a] Performed with 5 mol % catalyst.

identical chromatographic behaviors and that enone **23** could not be obtained in pure form. In addition, attempts at isomerizing cyclohexenone **24** to tricyclic enone **23** in the presence of metathesis catalyst **B** or **C** proved to be unsuccessful.

In an effort to circumvent the problem, it was found that the treatment of allylic alcohol compound **19** in CH_2Cl_2 at room temperature in the presence of catalyst **B** resulted in the formation of predominantly the two diastereomeric tricyclic allylic alcohols **25** and **26** (Scheme 4). Moreover, the extent of formation of allylic alcohol **27** was less than 10% isolated yield. Although these two tricyclic allylic alcohols could be separated by chromatography, the diastereomeric mixture of products thus obtained was directly oxidized to the desired tricyclic enone **23** using the product from **19** with R as either *i*-Pr or Ph.

Tricyclic enone **23** has proved to be an efficient dienophile in the stereo- and regioselective Diels−Alder reactions, and its use toward the synthesis of desogestrel (**1**) is currently under investigation.

Scheme 4. Synthesis of Tricyclic Enone **23**



In summary, we have developed an efficient route toward functionalized angularly fused tricycles, cyclopenta- and cyclohexa[*c*]indenes, by the use of the directed ROM−RCM reactions starting from readily available norbornen-7-one (**6**) via allyl- and homoallyl-tethered norbornene derivatives in 30% (nine steps) and 61% overall yields (six steps), respectively.

This ring-rearrangement strategy relies on an initial ruthenium−alkylidene species generated on the *syn*-alkenyl tether that can then be directed to activate the norbornene C=C bond, an otherwise unreactive site with *syn*-alkyl substitution. Following the highly favorable ROM of the norbornene C=C bond, the ensuing RCM of the resulting ruthenium species with the C=C bond of the enone or allylic alcohol completes the molecular rearrangement and affords the cyclopenta- or cyclohexa[*c*]indene system.

Supporting Information Available: Spectroscopic data of all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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