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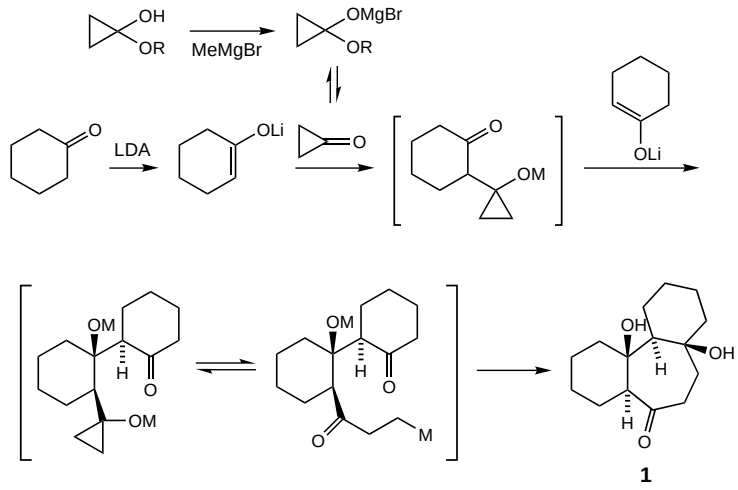
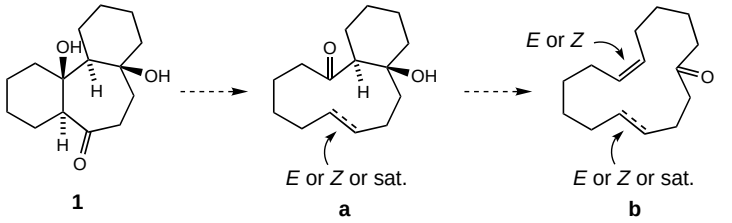


Scheme 1. Synthesis of ketone **1**.[5]



Scheme 2. Projected route to unsaturated C-15 macrocyclic ketones.

Access to C-15 Macrocyclic Ketones by Iterative Fragmentations of a Tricyclic System

Charles Fehr,* José Galindo, Olivier Etter, and Walter Thommen

In recent years, macrocyclic musks[1,2] have gained renewed interest for their excellent odor qualities (warm, sensual, animal, natural), and for their better biodegradability than benzenoid musks.[2,3]

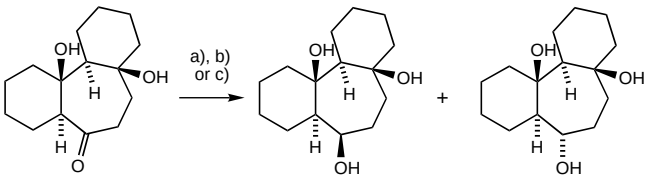
In particular, there is still a great need to find efficient syntheses for the construction of C-15 macrocyclic ketones possessing specific unsaturation. We herein report the first application of a new synthetic strategy in which the target compounds are obtained from an appropriately functionalized tricyclic system by two consecutive fragmentations. This approach is complementary to the metathesis-based annulations, which are often more direct but require high dilution and generally afford *E*/*Z* mixtures.[4]

Access to the targeted tricyclic fragmentation precursor was provided by the ready availability of the known dihydroxy ketone **1**, which was prepared in one pot from cyclohexanone and cyclopropanone (Scheme 1).[5] Despite a reported yield of 67%, it was only after modification of the experimental procedure that we were able to attain a reproducible yield of 44% (see Experimental Section).

The 1,3,5-functionalization of **1**, in which one oxygen atom is adjacent to a bridgehead and the two other oxygen atoms are situated at bridgehead positions, is ideally suited for cascade Grob fragmentations[6] and should allow, via intermediates **a**, ready access to new unsaturated C-15 macrocyclic ketones of type **b** (Scheme 2).

Reduction of **1** with $LiAlH_4$ afforded a 74:26 mixture of triols **2** and **3** (Scheme 3), whereas by using Red-Al® in THF at low temperature the all-*cis* triol **2** was obtained almost quantitatively in a highly diastereoselective manner (99:1). On the other hand, reduction with $BH_3{\cdot}SMe_2$ followed the opposite facial selectivity with an equally high diastereoselectivity (98:2), affording triol **3** in 81% yield (Scheme 3).[7]

For the conversion of alcohol **2** into tosylate **4**, whereas the application of classical conditions (TsCl, pyridine) gave rise to partial epimerization (by successive substitutions) and chloride formation, deprotonation of **2** with *n*BuLi followed by rapid treatment with TsCl gave the best results (Scheme 4).



a)	74	:	26	
b)	99	:	1	(98%)
c)	2	:	98	(81%)

Scheme 3. Diastereoselective reductions of ketone **1**. a) $LiAlH_4$ (1.15 equiv), THF, −70°C to −50°C; b) Red-Al® (3.0 equiv), THF, −70°C to room temperature; c) $BH_3{\cdot}SMe_2$ (0.71 equiv), THF, room temperature.

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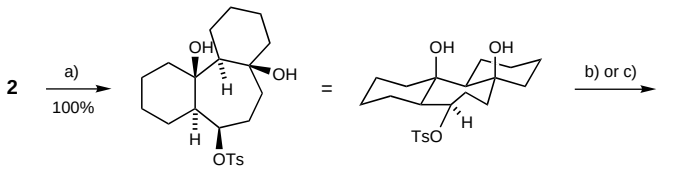
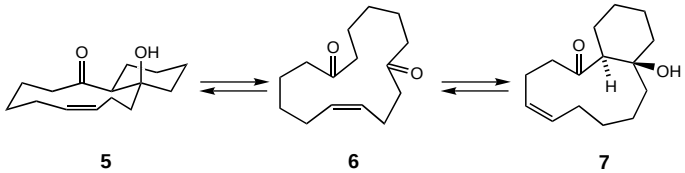
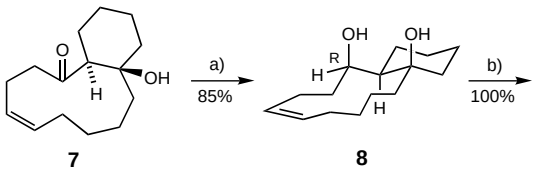


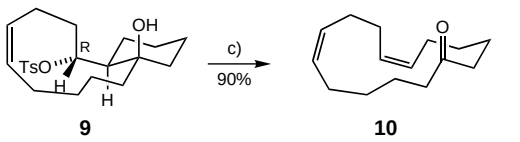


5 **6** **7**

b)	3%	15%	59%
c)	34%	15%	17%

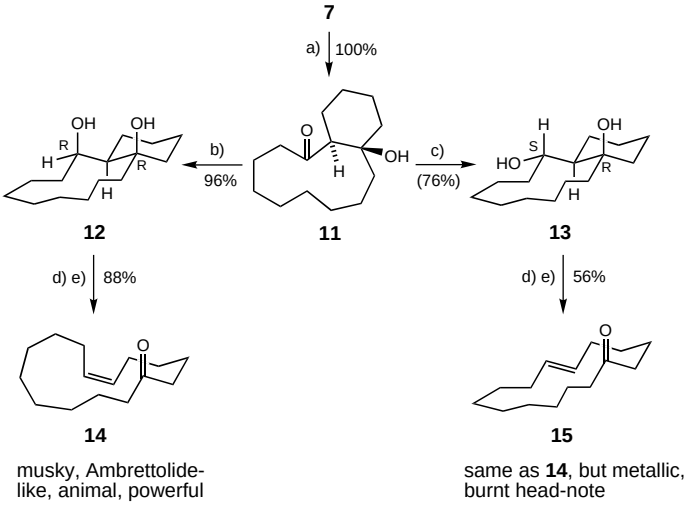
Scheme 4. Grob fragmentation of tosylate **4**: a) *n*BuLi (1.5 equiv), TsCl (1.15 equiv), THF, −15 °C, 20 min; b) KO*t*Bu (3 equiv), *t*BuOH, THF, −6 to 0 °C, 25 min; c) KO*t*Bu (3 equiv), DMF/THF (3:2), 0 to 15 °C, 15 min.





musky, greasy, waxy

Scheme 5. Conversion of **7** to the tosylate **9** and the subsequent Grob fragmentation to give (*Z*,*Z*)-6,10-cyclopentadecadienone **10**: a) $LiAlH_4$ (1.05 equiv), Et_2O; b) *n*BuLi (1.5 equiv), TsCl (1.15 equiv), THF, −15 °C, 20 min; c) KO*t*Bu (3 equiv), *t*BuOH, 25–29 °C, 10 min.



musky, Ambrettolide-like, animal, powerful

same as **14**, but metallic, burnt head-note

Scheme 6. Syntheses of (*Z*)-6- and (*E*)-6-cyclopentadecenones **14** and **15**: a) H_2, Pd (10 %)/C, cyclohexane; b) $LiAlH_4$ (1.2 equiv), Et_2O, RT; c) Red-Al® (4.0 equiv), THF, −78 °C to room temperature; d) *n*BuLi (1.5 equiv), TsCl (1.15 equiv), THF, −15 °C, 20 min; e) KO*t*Bu (3 equiv), *t*BuOH, 25–31 °C, 10 min.

Fragmentation of **4** was effected with KO*t*Bu in *t*BuOH/THF. To our surprise, only trace amounts (3 %) of the expected hydroxy ketone **5** were detected, the main product (59 % yield from **2**) being the isomeric hydroxy ketone **7**, in which the position of the C–C double bond is shifted by two carbon atoms. The concomitant formation of macrocyclic diketone **6**, isolated in 15 % yield, provided a clue for the explanation of the reaction course. This retroaldol product of **5** (and of **7**!) undergoes diastereoselective re-aldolization between two other centers to afford **7**. Indeed, reaction of **6** with KO*t*Bu in *t*BuOH also selectively furnished the more stable aldol **7**; assignment of the *trans* configuration for the ring junction is based on the similarity of the multiplicities of the ^{1}H NMR signals of the α-keto-methine group in **1**, **5**, and **7** (dd, J(H,H) = 4 and 12–13 Hz), and also on the fact that hydrogenation of a mixture of **5** and **7** gives **11** (see below) exclusively. This *trans* configuration of **6** was subsequently confirmed at a later stage of the synthesis (see acetonides **16** and **17**; Scheme 7). The *Z* configuration of the C–C double bond in **7** is in accord with the stereoelectronically imposed *trans*-antiperiplanar arrangement of the bridge C–C bond and the C–OTs bond in **4**. Incidentally, this is further proof for the all-*cis* relationship of the OH groups in **2**.

Interestingly, when the fragmentation was performed in DMF/THF,[6c] the initially formed **5** could be isolated as the major product (**5** + **7**: 51 %; **5**:**7** = 2:1), due to a slower re-aldolization.

A second sequence of reduction/tosylation/fragmentation was then applied to **7** (Scheme 5). Reduction with $LiAlH_4$ produced exclusively diol **8** in 85 % yield.[8] Subsequent tosylation followed by fragmentation afforded (*Z*,*Z*)-6,10-cyclopentadecadienone **10** in 90 % yield (two steps).

The attractiveness of our synthetic plan lies in its flexibility: any 3-hydroxy ketone can in principle be converted into either a *Z*- or an *E*-unsaturated ketone, depending on the stereochemical outcome of the reduction (*syn* or *anti*). This is illustrated by the synthesis of (*Z*)-6- and (*E*)-6-cyclopentadecenone **14** and **15**. Our common starting point was hydroxy ketone **11**, which was readily prepared by hydrogenation of **7** (Scheme 6). Reduction of **11** using $LiAlH_4$ afforded **12** with excellent diastereoselectivity (97:3) and 96 % yield. $BH_3{\cdot}SMe_2$ (0.7 equiv) in THF at room temperature was also highly selective (> 99:1), but showed low reactivity (34 % conversion).[9]

An opposite mode of reduction was observed by using Red-Al®. Whereas reduction at room temperature only moderately favored the (*S*,*R*)-diol **13** (**13**:**12** = 70:30), reduction at −70 °C produced **13** selectively (**13**:**12** = 92:8 to 95:5).[7] Unfortunately, the reaction did not go to completion (76 % yield based on conversion (74 %)), and 16 % of 1,7-cyclopentadecadione was also formed by retro-aldol condensation (perhaps during workup).

Tosylation of **12** and fragmentation afforded (*Z*)-6-cyclopentadecenone **14** in high yield (88 %; 52 % from **1**) with complete stereocontrol. Unexpectedly, the synthesis of **15** from **13** proved more difficult, due to the instability of the intermediate tosylate, which, in competition with the stereocontrolled fragmentation (56 % yield), also undergoes elimination reactions.

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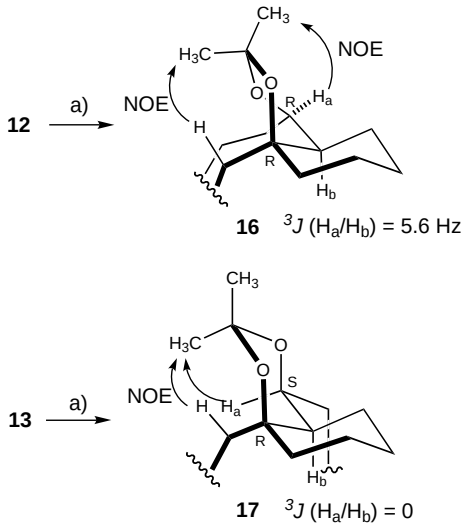
The stereospecific course of the fragmentation reactions (**12** to **14** and **13** to **15**) lends additional support to the configurations attributed to **12** and **13**, although inversion of *both* stereogenic centers which ultimately become sp^2-carbon atoms, would lead to *the same* fragmentation product. Therefore, for further corroboration of the attributed structures, **12** and **13** were converted into their acetonides **16** and **17**. The measured ^{1}H NMR coupling constants and NOE effects are perfectly in agreement with the postulated structures, as drawn in their most stable conformations (MM2 calculations) (Scheme 7).



Scheme 7. Structure determination of acetonides **16** and **17**: a) 2-methoxypropene, cat. TFA, DMF, 25 °C, 3 h.

All three unsaturated macrocyclic ketones **10**, **14**, and **15** are new[10] and possess the typical musk odor; in particular, **14** represents an excellent, powerful musk odorant.

Experimental Section

Tricyclic ketone **1**: Modified version of the procedure published in reference [5]. Under mechanical stirring, a solution of MeMgBr in *Et_2O* (!) (Aldrich, 3 N; 44.7 mL, 134.0 mmol) was added dropwise at 25–28 °C (water-bath cooling) to a solution of cyclopropanone ethyl hemiacetal[11] (containing variable amounts of cyclopropanone methyl hemiacetal) (11.07 g, ca. 111.7 mmol) (methyl/ethyl ca. 3:1; 92 % pure) in Et_2O (305 mL). Gas evolution (methane) and the formation of a white precipitate were observed. After 10 min, the suspension was treated (by using a cannula; introduction time: ca. 2 min) with a solution of deprotonated cyclohexanone (from cyclohexanone (10.95 g, 111.7 mmol) in THF (74 mL) and LDA (117.3 mmol; from HN*i*Pr$_2$ (12.44 g, 17.14 mL, 123.2 mmol), *n*BuLi (1.48 N in hexane, 79.3 mL, 117.3 mmol) in THF (187 mL); −78 °C to RT). The temperature was maintained below 30 °C. After 2 h, the almost clear reaction mixture was treated at 18–20 °C with saturated NH_4Cl solution (180 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2. Washing of the organic layers (H_2O, then sat. aq. NaCl), drying (Na_2SO_4) and concentration afforded 15.5 g of a partly crystallized oil. Upon addition of Et_2O (75 mL), ketone **1** precipitated. The suspension was stored at 0 °C for 15 h and filtered. Yield of **1**: 6.22 g (44 %) of a white solid, whose analytical data were identical with those reported. ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 2.89$ (dd, J(H,H) = 13 and 4 Hz, 1 H; CH−CO), 2.71 (ddd, J(H,H) = 16, 12 and 6 Hz, 1 H; CH_2−CO), 2.36 ppm (ddd, J(H,H) = 16, 6 and 3 Hz, 1 H; CH_2−CO).

Triol **2**: A solution of Red-Al® (= Vitride® = $NaAlH_2(OCH_2CH_2OCH_3)_2$; ca. 70 % in toluene) (40.56 g, 140.5 mmol)) in THF (70 mL) was added in 40 min to a solution of **2** (11.81 g, 46.9 mmol) in THF (330 mL) at −70 °C. The reaction mixture was allowed to reach room temperature (2 h) and was then quenched at 15–20 °C with 5 % aqueous NaOH (280 mL), and **2** was extracted twice with EtOAc. Washing (H_2O, $NaHCO_3$, then sat. aq. NaCl), drying (Na_2SO_4), and concentration of the filtrate afforded a white solid (11.73 g, yield 98 %) consisting of **2** (**2**:**3** = 99:1). ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 3.86$ ppm (m, J(H,H) = 4 Hz + smaller couplings, 1 H; CH−O).

Triol **3**: $BH_3{\cdot}SMe_2$ (136 mg, 0.170 mL, 1.70 mmol) was added at room temperature to a stirred solution of **1** (600 mg, 2.40 mmol) in THF (20 mL). After 15 h, MeOH (10 mL) and 5 % aqueous NaOH (10 mL) were added. The reaction mixture was stirred for 3 h and concentrated at the rotavapor (60 °C/50 Torr). The remaining aqueous phase was treated with saturated aqueous NaCl (40 mL) and the product was extracted twice with AcOEt. Washing (H_2O, then sat. aq. NaCl), drying (Na_2SO_4), and concentration of the filtrate afforded a white solid (0.495 mg, yield 81 %) consisting of **3** (**3**:**2** = 98:2). ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 3.41$ ppm (m, J(H,H) = 9 Hz, 4 Hz + smaller couplings, 1 H; CH−O).

Tosylate **4**: A solution of *n*BuLi in hexane (1.48 M, 59.7 mL, 88.4 mmol) was added at 25 °C to a solution of **2** (11.23 g, max. 44.2 mmol) in THF (678 mL). The solution was stirred at 40 °C for 15 min, cooled at −18 °C, and treated at once with TsCl (9.68 g, 50.8 mmol). After 20 min at −15 °C, the mixture was poured into 5 % aqueous HCl, and **4** was extracted with AcOEt in the usual manner. Yield: 18.36 g of a white-ocher powder (100 %).

Preparation of **7** by fragmentation: KO*t*Bu (14.29 g, 127.7 mmol) was added in one portion to a solution of **4** (17.36 g, max. 42.5 mmol) in *t*BuOH (340 mL) and THF (170 mL). The temperature was maintained between −6 and 0 °C by means of a NaCl/ice–water bath (−9 °C). After 25 min, the mixture was poured into 5 % aqueous HCl and the products were extracted with Et_2O in the usual manner to afford an oil, consisting of **7** and **6** (11.15 g; ca. 4:1). Flash chromatography (SiO_2 (250 g); cyclohexane/AcOEt = 95:5) afforded **7** (6.20 g; containing 4–5 % of an unknown isomer and 3 % of **5**; 62 % yield) and **6** (1.49 g; 15 %). ^{1}H NMR (360 MHz, $CDCl_3$) of **7**: $\delta = 5.48$ (m, 1 H; CH=), 5.27 (m, 1 H; CH=), 2.62 (dd, J(H,H) = 13 and 4 Hz, 1 H; CH−CO), 2.60 (dist. t, J(H,H) = 11 Hz, 1 H; from CH_2−CO), 2.35–2.53 (m, 2 H; CH_2C=), 2.15–2.28 (m, 2 H; 1 H from CH_2−CO + 1 H from CH_2C=), 1.90–2.03 ppm (m, 1 H; from CH_2C=); ^{13}C NMR (360 MHz, $CDCl_3$): $\delta = 131.5$ (d), 128.7 (d), 24.7 and 24.3 ppm (t of allylic C).

Preparation of **5** (containing **7**) by fragmentation: Repetition of the above conditions in DMF/THF (3:2) at 0 to 15 °C for 15 min afforded a mixture enriched in **5** (**5**:**7** ca. 66:34), together with about 20 % of diketone **6**. Chromatographic purification (SiO_2; cyclohexane/AcOEt = 95:5) afforded a 65:35 mixture of **5** and **7**. ^{1}H NMR (360 MHz, $CDCl_3$) of **5**: δ = ca. 5.37–5.50 (m, 2 H; CH=CH)), 2.93 (dd, J(H,H) = 12 and 4 Hz, 1 H; CH−CO), 2.84 (ddd, J(H,H) = 13, 8, and 4 Hz, 1 H; from CH_2−CO), 2.33–2.42 ppm (m, 1 H; from CH_2−CO); ^{13}C NMR (360 MHz, $CDCl_3$): $\delta = 130.6$ (d), 129.8 ppm (d).

Characteristic data of **10**: GC: ca. 90 % pure; contains two other isomers (*E,Z* isomer of **10** + unknown isomer). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.32–5.48 (m, 4 H; CH=), 2.42 ppm (t, J(H,H) = 7 Hz, 4 H; CH_2CO)); ^{13}C NMR (360 MHz, $CDCl_3$): $\delta = 129.9$ (d), 129.3 (d), 28.2 and 26.1 ppm (t of allylic C); coalescent signals due to the symmetry of **10**.

Characteristic data of **11**: GC: ca. 98 % pure; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 2.88$ (d, J(H,H) = 12 and 4 Hz, 1 H; CH−CO), 2.48 (m, 1 H; CH_2−CO), 2.25 ppm (m, 1 H; CH_2−CO).

Characteristic data of **12**: GC: ca. 96 % pure; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 3.56$ ppm (dt, J(H,H) = 12 and 4 Hz, 1 H; CH−O).

Characteristic data of **13**: GC: ca. 96 % pure; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 4.25$ ppm (br s, 1 H; CH−O).

Characteristic data of **14**: M.p. 35–36 °C; GC: ca. 96 % pure; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 5.35$ (m, 2 H; CH=), 2.35–2.45 ppm (m, 4 H; CH_2COCH_2); ^{13}C NMR (360 MHz, $CDCl_3$): $\delta = 130.7$ (d), 129.5 (d), 26.6 and 26.2 ppm (t of allylic C).

Characteristic data of **15**: GC: ca. 96 % pure; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 5.32$ (m, 2 H; CH=), 2.30–2.42 ppm (m, 4 H; CH_2COCH_2); ^{13}C NMR (360 MHz, $CDCl_3$): $\delta = 131.9$ (d), 130.6 (d), 31.8 and 31.7 ppm (t of allylic C).

Acetonide **16**: A solution of diol **12** (50 mg, 0.21 mmol) and 2-methoxypropene (0.1 mL; ca. 5 equiv) in DMF (1.3 mL) was treated at 25 °C with

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trifluoroacetic acid (0.012 mL). After stirring for 3 h, NEt_3 (three drops) and AcOEt (20 mL) were added. The solution was poured into saturated aqueous $NaHCO_3$, the phases were separated, and the organic phase was washed (sat. aq. NaCl), dried (Na_2SO_4), and concentrated. Yield: 50 mg (85%).^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 3.67$ ppm (dd, J(H,H) = 6.2 and 5.65 Hz (coupling with 1 H of CH_2 and with CH), 1 H; CH–O).

Characteristic data of **17**: ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 4.29$ ppm (dd, J(H,H) = 9.5 and 4 Hz (coupling with CH_2), 1 H; CH–O).

Received: July 9, 2002 [Z19697]

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[4] Recent example: R. Hamasaki, S. Funakoshi, T. Misaki, Y. Tanabe, *Tetrahedron* **2000**, *56*, 7423. As mentioned by a referee, the selectivity problem could be solved by metathesis of an appropriate non-terminal diacetylene. See: A. Fürstner, G. Seidel, *Angew. Chem.* **1998**, 110, 1758; *Angew. Chem. Int. Ed.* **1998**, *37*, 1734.

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[7] The factors that govern "internal" versus "external" hydride attacks are not yet fully understood.

[8] Here, Red-Al® reduction at room temperature led to a 43:57 diastereomeric mixture of alcohol **8** and its diastereomer (85%). At −70 °C no reduction was observed.

[9] This reaction was not tested with larger amounts of reagent.

[10] However, the *E*,*E* and *E*,*Z* isomers of **10** have been synthesized: G. Büchi, H. Wüest, *Helv. Chim. Acta* **1979**, *62*, 2661.

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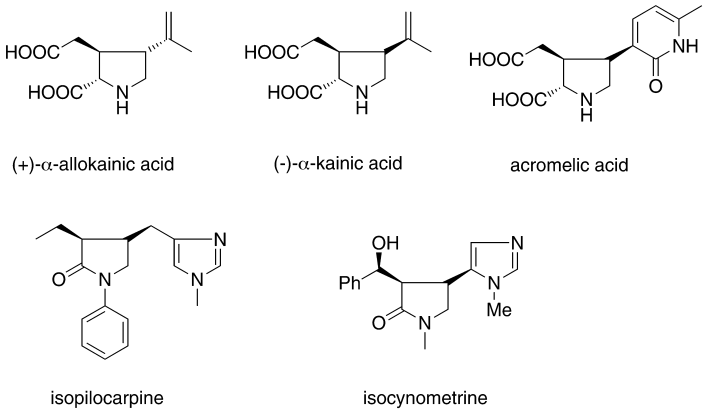
Highly Enantioselective Cycloisomerization of Enynes Catalyzed by Rhodium for the Preparation of Functionalized Lactams**

Aiwen Lei, Jason P. Waldkirch, Minsheng He, and Xumu Zhang*

The rising demand for chiral raw materials, intermediates, and active ingredients in pharmaceuticals, agrochemicals, food additives, and fragrances provides the impetus for rapid developments in chiral technology.[1] It remains a huge challenge for organic chemists to develop highly enantioselective reactions for the preparation of enantiomerically pure compounds in a cost-effective manner. Lactams are a versatile motif in organic chemistry and when functionalized, lactams often either show biological activity themselves, or are important building blocks for biologically active molecules such as (+)-α-allokainic acid, (+)-α-kainic acid,[2] acromelic



acid,[3] isopilocarpine,[4] and isocynometrine.[5] Generally, lactams are synthesized by intramolecular C–N bond formation. However, this method for the synthesis of enantiomerically pure and functionalized lactams requires that the chiral centers and functional groups must be assembled in advance. Therefore, methodology that allows enantioselective carbon–carbon bond formation for the generation of functionalized lactams without presetting the chiral centers will be a significant advance in synthetic organic chemistry.

The transition-metal-catalyzed intramolecular Alder-ene-type reactions of enynes are well-developed[6] and provide efficient entries to a variety of useful functionalized carbocyclic[7] and heterocyclic compounds.[8] However, the number of lactam preparations reported involving the transition-metal-catalyzed cycloisomerization of enynes is limited. In fact, the literature contains only a single example describing a palladium-catalyzed cycloisomerization of alkynyl *N*-acyl enamines.[9] Very recently, a mechanistically different palladium(II)-catalyzed synthesis of α-alkylidene-γ-butyrolactams was reported.[10] Previously, we have discovered a Rh-catalyzed cycloisomerization of enynes and developed its asymmetric version.[11] Although this was a substrate- and ligand-dependent reaction, up to 96% *ee* was achieved.[11b] This led us to consider strategies for expanding the scope of the reaction as well as improving the enantioselectivity. We report herein the results of this effort: in an efficient, mild, and general route to synthesize a variety of lactams in high enantioselectivity using a catalyst derived from a commercially available metal precursor [{Rh(cod)Cl}$_2$] and the ligand binap.[12]

Initially, the reaction was studied with unprotected enyne amides (Scheme 1, $R^3 = H$) as the cycloisomerization substrates. However, none of the desired cyclization products were detected and the starting materials were recovered. The negative results may be because the *trans*-isomer of this type of unprotected enyne amide is dominant, which would be unfavorable for the cycloisomerization (Scheme 1).[13] There-

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