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Supramolecular Photochirogenesis with Carbenes Entrapped in Cyclodextrins[‡]

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Two achiral diazirines **1a** and **1b** have been encapsulated in the inherently chiral cavity of α-cyclodextrin (**6-Cy**), β-cyclodextrin (**7-Cy**) and permethylated β-cyclodextrin (**TRIMEB**) and photolyzed. Because of supramolecular photochirogenesis the generated carbenes afford intramolecular C–H insertion products not as a racemate but one enantiomer is slightly favored. With **1a@(6-Cy)$_2$** the *ee* of product **7a** is doubled. To the best of our knowledge for the first time for carbene reactions, products are imprinted, though modestly, with handedness derived from **Cy**s. The reaction of **1b** is highly dependent on the molecular reactor used for inclusion. Whereas **7-Cy** is very efficient for favoring dimerization through azine formation, the use of **TRIMEB** permits exclusive formation of intramolecular insertion product **7b**.
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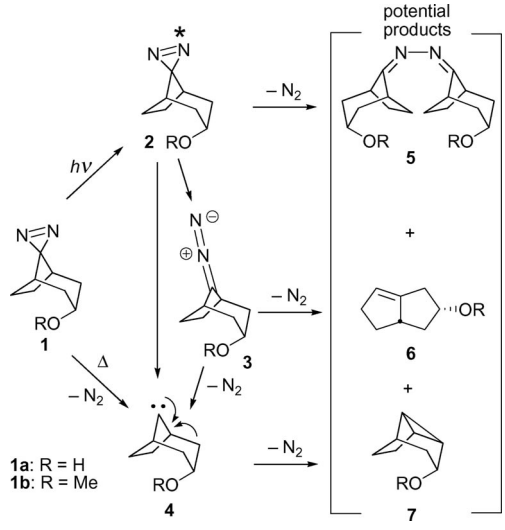
Introduction

It is often useful to perform a reaction in a constrained system.[1] For example, zeolites are employed on a large scale to force the isomerization of hydrocarbons in stereotype patterns, amongst others.[2] Indeed, the use of a host molecule as a reaction vessel opens up the possibility to synthesize products that would be difficult to obtain in solution[3] or to modify the course of a reaction.[4] This technique can also be applied to the generation of reactive molecules which might get bottleable if they are incarcerated in a host molecule.[5] It is particularly meaningful to perform carbene reactions in a molecular reactor because of the high reactivity of the divalent carbon atom. In fact, methylene has been described as the most indiscriminating reagent in chemistry.[6] Even if all other carbenes are partly stabilized and therefore more selective,[7] they still tend to generate product mixtures. This is especially true for C–H insertion reactions by which only stabilized carbenes like the nucleophilic foiled carbenes[8] or the electrophilic dihalocarbenes[9] give synthetically useful results. For more reactive carbenes, encapsulation in a cavitand permits to reduce the mobility of the intermediate, therefore lessening the number of accessible bonds or lone-pairs that may act as reaction partners and consequently, reducing the amount of side-products. Moreover, the equilibrium conformation of a guest molecule can also be modified.[10] This may permit to considerably change the outcome of an intramolecular C–H insertion reaction.

In this paper we report about the inclusion of *endo*-spiro-[bicyclo[3.2.1]octane-8,3′-[3*H*]diazirin]-3-ol (**1a**) and *3-endo*-methoxyspiro[bicyclo[3.2.1]octane-8,3′-[3*H*]diazirine] (**1b**) in β-cyclodextrin (**7-Cy**), heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (**TRIMEB**), and α-cyclodextrin (**6-Cy**) (Scheme 1). We will show what kind of consequence the local geometry at the reaction center has over the course of the reaction and why different products are obtained. Moreover, the rearrangement of carbene **4** induces a loss of symmetry in the expected products **6** and **7**. Thus, if this reaction is performed in the chiral cavity of a cyclodextrin, chirality might be imparted to the carbene products.[1e] Will one of the enantiomers of **6** and **7** be formed in excess?



Scheme 1. Potential reactions of diazirines **1**.

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Results

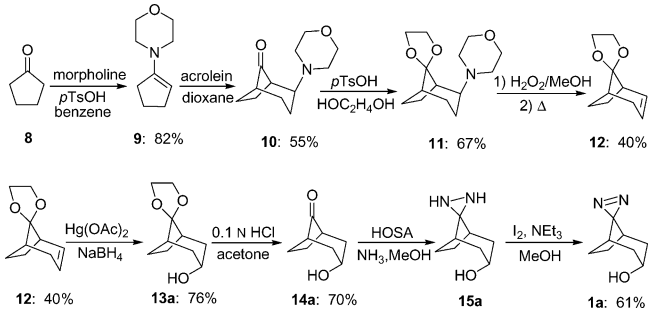
Photolyses in the Solid State

Photolysis of **1a@TRIMEB** in the solid state leads exclusively to the formation of tricyclooctanol **7a**[11] and bicyclooctenol **6a** (Scheme 1) in a ratio of 79:21 (Table 1) as determined by ^{1}H NMR spectroscopy of the crude reaction mixture. Since the Cy′s chiral recognition ability is low in general, a small enantiomeric excess (*ee* = 4%) was determined by chiral HPLC for the formation of **7a**. With **1a@7-Cy**, the outcome of the reaction is significantly different: **7a** and **6a** are now formed in a ratio of 55:45. Moreover, although the *ee* remains the same (4%), now the other enantiomer of **7a** is formed preferentially. The highest selectivity is observed with α-cyclodextrin, a smaller and less flexible host: photolysis of **1a@(6-Cy)$_2$** leads to the formation of **7a** and **6a** in a ratio of 45:55, while the *ee* for **7a** doubles to 8%.

Table 1. Product distribution.

	5/14	6/7	*ee* 7
1a@7-Cy		45:55	4%
1a@TRIMEB		21:79	4%
1a@(6-Cy)$_2$		55:45	8%
1a		34:66	
1b@7-Cy	89:11		
1b@TRIMEB		**7b**[11] exclusively	
1b		36:64	
1b in benzene	38:5	15:42	

More significant differences in the chemoselectivity were observed from the photolyses of **1b**. In **7-Cy** the product consists of a mixture of azine **5b** (89%) and ketone **14b** (11%) (Scheme 2). In contrast, with **1b@TRIMEB**, tricyclooctane **7b**[11] is the sole product obtained from an intramolecular insertion of carbene **4b** and no bicyclooctene **6b** is formed. As can be seen from these results, the composition of the products strongly depends on the host molecule and thus can be explained by a corset effect caused by the size of the reaction vessel.



Scheme 2. Synthesis of carbene precursor **1a**.

For comparison purposes, experiments have been performed using a classical approach: photolysis of **1b** in a diluted solution (0.042 M) in benzene affords **6b** and **7b** in a ratio of 15:42. Under these conditions bimolecular reactions leading to formation of azine **5b** are difficult to avoid and 38% of **5b** are obtained as side-product. Gas phase pyrolysis solves this problem giving only intramolecular reactions: **1b** produces **6b** and **7b** in a ratio of 36:64 (34:66 for **1a**). At this point it is worth noticing that the unsubstituted bicyclo[3.2.1]octan-8-ylidene exclusively yields the C–H insertion product.[12] The main reason for this difference in reactivity resides in steric hindrance between the axial *endo*-substituent with the C_2H_4 bridge which favors the rearrangement to the somewhat flat bicyclo[3.3.0]skeleton in order to release this strain.

Discussion

From a mechanistic point of view, it is known that by thermal decomposition of most diazirines, carbenes are directly generated.[13] By photolysis, however, the situation is more complex (Scheme 1). After excitation, diazirine **2** can either directly form the final products, a process coined RIES (Rearrangement In the Excited State),[14] generate carbene **4** or ring-open to diazo compound **3**,[15] an intermediate that often can engender similar products than the carbene. Cyclodextrins are particularly well suited as hosts for carbene reactions, since it has been shown that the divalent carbon atom in alkylidenes does not interact with ethereal oxygen[16] precluding the intermediacy of an oxonium ylide. In preliminary communications,[17] we have described the complex of **1a** with **TRIMEB** in solution and in the solid state. Because of the lack of intramolecular hydrogen bonds, **TRIMEB** is more flexible and is better soluble in water than **7-Cy**. For the **1a@TRIMEB** complex, it follows that the association constant with $K = 460\ M^{-1}$ is about one-twentieth lower than the one of **1a@7-Cy** owing to the higher flexibility of **TRIMEB**. Nonetheless, for a guest that is slightly soluble in water, this is still a fairly high value. The advantages of **TRIMEB** over **7-Cy** are a better solubility of the complexes (**7-Cy** complexes tend to be poorly soluble) and a larger size of the crystals obtained which facilitates structure analysis and identification of the products resulting from photolysis. In contrast, if **7-Cy** is used as reaction vessel, the alkyl carbene to a significant amount may also insert into the O–H bonds of the host,[18] a process that also explains the low recovery of products after irradiation of **1b@7-Cy**. But since **TRIMEB** does not possess functional groups or bonds which are susceptible to react easily with a relatively nucleophilic alkyl carbene,[7] **1a** only can rearrange intramolecularly, affording *endo*-tricyclo[3.3.0.0^{2,8}]octan-3-ol (**7a**)[19] and bicyclo[3.3.0]oct-5-en-3-ol (**6a**)[20] in a ratio depending on the host molecule used. In the case of **1a@TRIMEB**, the larger size of the cavity also allows a total separation of one guest molecule from another. The generated carbene then is surrounded by the host only. Figure 1 shows the crystal structure obtained for **1a@TRIMEB**. The driving force for the formation of this inclusion complex is the filling of the empty space inside the cavity of **TRIMEB** by the suitably sized guest. In addition, the orientation of the diazirine is partly controlled by a hydrogen bond between the hydroxy group of the guest and a glucosidic oxygen atom of the host.

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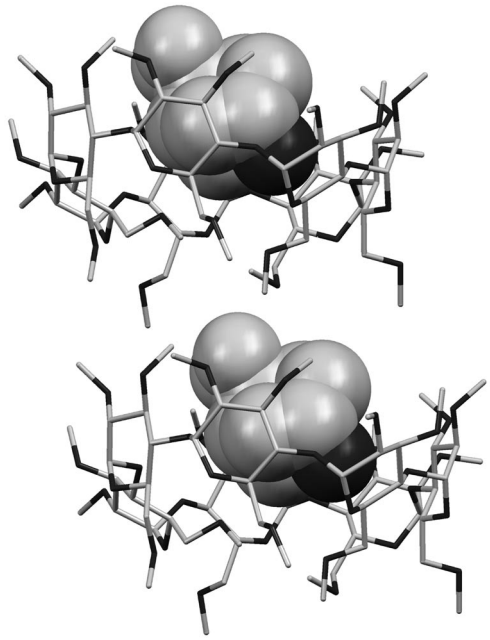


Figure 1. Crystal structure of **1a@TRIMEB** showing the packing of the complex.[17b] The hydrogen atoms are omitted for clarity.

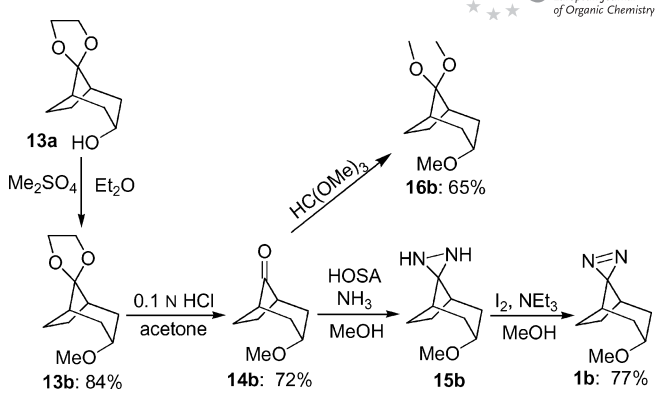
In contrast, however, in **1b@7-Cy**, in the solid state, the diazirine groups are probably positioned in a head-to-head arrangement. This is the most plausible explanation for the fact that high yields of azine **5** are obtained. The in situ generated carbene is directly and efficiently trapped by a second diazirine in a barrier-free process forming a diazirinium ylide that concomitantly rearranges to the corresponding azine.[21]

Synthesis of the Diazirines

Both carbene precursors used in this study were synthesized from ketal **13a** as depicted in Scheme 2 following procedures developed previously.[22–24] Alternatively, compound **14a** is also accessible from a reaction between 1-cyclopentenylpyrrolidine and 3-chloro-2-(chloromethyl)-1-phenylpropan-1-one.[25,26]

Diazirine **1a** was obtained in good yield (61%, 2 steps) by treatment of ketone **14a** with ammonia and hydroxylamine sulfonic acid (HOSA) in methanol followed by oxidation with iodine and triethylamine in methanol.

Diazirine **1b** was prepared by an analog procedure after methylation of ketal **13a** with dimethyl sulfate (Scheme 3). We have optimized the removal of the ketal group which proceeds more cleanly in aqueous acetone with 0.1 N HCl. If the reaction is performed in an acidic methanol/water mixture as described in the literature, the crude product tends to be contaminated by significant amounts of dimethyl ketal **16a**. Dimethyl ketals **16a** and **16b**, respectively, are also formed in traces as side-products in the diazirine synthesis. The identity of byproducts **16** was determined by independent syntheses, i.e., treatment of ketones **14** with trimethyl orthoformate.



Scheme 3. Synthesis of carbene precursor **1b**.

Conclusions

The utilization of TRIMEB as a molecular reactor for a carbene reaction instead of native cyclodextrin offers significant advantages: it permits to avoid reaction of the carbene with the O–H bonds of the cyclodextrin rims. In the case of **1b**, it also prevents the formation of dimeric azine because the larger size of the cavity allows to fully enclose the carbene precursor and to separate it from other precursor molecules. Moreover, to the best of our knowledge for the first time for carbene reactions within α- and β-cyclodextrins, a modest enantioselectivity for the product formation has been observed. The imprinted chirality was highest when the reaction was performed in the smaller cavity of α-cyclodextrin.

Experimental Section

General Methods: Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. $CDCl_3$ or [D_6]DMSO were used as solvents. The chemical shifts at δ = 7.26 ppm and 77.0 ppm of $CHCl_3$ were used as internal standards for ^{1}H and ^{13}C spectra, respectively (2.50 and 39.43 for DMSO). Conventional 2D COSY, NOESY, HMBC, and HMQC spectra were used to derive proton and carbon assignments. When necessary, 1D TOCSY spectra were also recorded.

General Procedure for the Preparation of the Complex: The cyclodextrin was dissolved in a minimal amount of water. Neat diazirine **1** (1 equiv.) was added to the solution, ultrasonicated for 1 min, and stirred for 1 h. The suspension was suction-filtered through a sintered glass funnel (porosity 4 frit). The residue was washed with water and dried.

General Procedure for the Photolysis in the Solid State: The complexes were photolyzed with a Heraeus TQ718-Z4, 700 W lamp (doped with FeI_2) in Pyrex glassware after the flask has been alternately evacuated and filled with argon for three times. The crude products were analyzed by NMR spectroscopy and GC-MS after separation from the host molecule.

1a@7-Cy (643 mg, 0.5 mmol) was photolyzed overnight at 12 °C. The powder was then submitted to continuous extraction with dichloromethane yielding 65 mg (ca. 94% recovery) of products derived from the guest. NMR analysis revealed the presence of tricyclooctanol **7a** and bicyclooctenol **6a** in a ratio of 55:45. Chiral HPLC [Chiracel OD-H column (Column Nr.: ODH0CE-GJ020),

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hexanes/2-propanol 98:2, 0.7 mL/min, T = 20 °C, RID] allowed the quantification of the enantiomeric excess for **7a**: enantiomer 1, t_R = 14.1 min, 48%; enantiomer 2, t_R = 15.1 min, 52%.

1a@TRIMEB (1582 mg, 1 mmol) was photolyzed overnight at 12 °C. NMR of the crude product showed the absence of diazirine **1a** and the presence of tricyclooctanol **7a** and bicyclooctenol **6a** in a ratio of 79:21. Column chromatography with CH_2Cl_2 followed by hexanes/Et_2O (50:50) lead to the isolation of 52 mg (0.42 mmol, 42%) of **7a**. Chiral HPLC [Chiracel OD-H column (Column Nr.: ODH0CE-GJ020), hexanes/2-propanol 98:2, 0.7 mL/min, RID] allowed the quantification of the enantiomeric excess: enantiomer 1, t_R = 14.1 min, 52%; enantiomer 2, t_R = 15.1 min, 48%.

1a@(6-Cy)$_2$ (1.11 g, 0.53 mmol) was photolyzed at 12 °C for 16 h. NMR of the crude product showed the presence of tricyclooctanol **7a** and bicyclooctenol **6a** in a ratio of 45:55. Extraction with CH_2Cl_2 followed by chromatography (hexanes/Et_2O, 50:50) lead to the isolation of 7.5 mg (0.06 mmol, 11%) of **7a**. Chiral HPLC [Chiracel OD-H column (Column Nr.: ODH0CE-GJ020), hexanes/2-propanol 98:2, flow: 0.7 mL/min, RID] allowed the quantification of the enantiomeric excess: enantiomer 1, t_R = 14.2 min, 54%; enantiomer 2, t_R = 15.3 min, 46%.

1b@7-Cy (382 mg, 0.294 mmol) was photolyzed overnight at 12 °C. The powder was then extracted with dichloromethane, yielding 13 mg of product (44% recovery) consisting of a mixture of 89% azine **5b** and 11% of ketone **14b**.

1b@TRIMEB (929 mg, 0.582 mmol) was photolyzed overnight at 12 °C. NMR of the crude product shows the absence of diazirine **1b** and bicyclooctene **6b**. Column chromatography with pentane/Et_2O (90:10) lead to the isolation of 29 mg (0.21 mmol, 36%) of **7b**.

Photolysis of Diazirine 1b in Benzene: Diazirine **1b** (105 mg, 0.63 mmol) was dissolved in 15 mL of benzene. The solution was degassed and irradiated for 3 h at 12 °C. The solvent was rotary-evaporated, yielding 83 mg of a mixture containing 38% of azine **5b**, 42% of 3-*endo*-methoxytricyclo[3.3.0.0^{2,8}]octane (**7b**), 15% of *rac*-(1*R*,3*S*)-3-methoxybicyclo[3.3.0]oct-5-ene (**6b**), and 5% of ketone **14b**.

Pyrolysis of *endo*-Spiro[bicyclo[3.2.1]octane-8,3′-[3*H*]diazirine]-3-ol (1a): A three-necked round-bottomed flask was equipped with a small distillation bridge with a cooling trap (–78 °C). The flask was heated to 330 °C and 100 mg of diazirine **1a** were slowly dropped under vacuo, affording 54 mg (66%) of a mixture of 66% of *endo*-tricyclo[3.3.0.0^{2,8}]octan-3-ol (**7a**) and 34% of *rac*-(1*R*,3*S*)-bicyclo[3.3.0]oct-5-en-3-ol (**6a**).

Pyrolysis of 3-*endo*-Methoxyspiro[bicyclo[3.2.1]octane-8,3′-[3*H*]diazirine] (1b): A three-necked round-bottomed flask was equipped with a small distillation bridge with a cooling trap (–78 °C). The flask was heated to 260 °C and 41 mg of diazirine **1b** were slowly dropped under an argon stream, yielding 20 mg (48%) of a mixture of 64% of **7b** and 36% of **6b**.

***endo*-Spiro[bicyclo[3.2.1]octane-8,3′-[3*H*]diazirine]-3-ol (1a):**[16] 3-*endo*-Hydroxybicyclo[3.2.1]octane-8-one (**14a**) (2.91 g, 20.8 mmol) was stirred in a 8 M solution of NH_3 in MeOH at –30 °C for 2 h. The temperature then was lowered to –60 °C and 1 equiv. of hydroxylamine-*O*-sulfonic acid (HOSA) was added in portions during 1 h. The reaction mixture was stirred overnight, making sure that the temperature only slowly increased. Methanol and ammonia were then rotary evaporated. The residue was dissolved again in 70 mL of MeOH. NEt_3 (5 mL) was first added and I_2 was added in portions until no decolorization took place. The excess of I_2 was reduced with $Na_2S_2O_5$ and methanol was partially rotary evaporated. The methanol solution was then diluted with water and brine and extracted three times with pentane, yielding 1.409 g of product. Another crop of 0.505 g was obtained through extraction of the water phase with CH_2Cl_2 and column chromatography with hexanes/ethyl acetate (70:30). Total yield 1.914 g (61%) m.p. 144–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, J = 3.1 Hz, 2 H, H^1 + H^5), 1.38 (s, 1 H, OH), 1.88 (d-hept, J = 14.9, 1.2 Hz, 2 H, H$^2_{endo}$ + H$^4_{endo}$), 2.06–2.16 (m, 4 H, H^6 + H^7), 2.24 (ddd, J = 14.9, 4.8, 3.2 Hz, 2 H, H$^2_{exo}$ + H$^4_{exo}$), 4.28 (t, J = 4.8 Hz, 1 H, H$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3, 36.3, 38.3, 41.8, 66.6 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3612, 2942, 2921, 2888, 2848, 1574, 1288, 1253, 1228, 1190, 1076, 1050, 1029 cm^{-1}. MS (EI): *m*/*z* (%) = 152 (M$^+$) [0.01], 151 (0.01), 124 (0.1), 123 (0.7), 109 (4), 105 (4), 95 (11), 91 (22), 80 (40), 79 (100). MS (CI): *m*/*z* = 153, 135, 123, 107 (100), 79. HRMS: calcd. for $C_8H_{12}O$ (M$^+$ – N_2): 124.0888, found 124.0892.

3-*endo*-Methoxyspiro[bicyclo[3.2.1]octane-8,3′-[3*H*]diazirine] (1b): 3-*endo*-Methoxybicyclo[3.2.1]octan-8-one (**14b**) (2.821 g, 18 mmol) was stirred in a 8 M solution of NH_3 in MeOH at –30 °C for 3 h. The temperature then was lowered to –60 °C and 1 equiv. of HOSA was added in portions during 1 h. The reaction mixture was stirred overnight, making sure that the temperature only slowly increased. Methanol and ammonia were then rotary evaporated. The residue was dissolved again in 70 mL of MeOH. After addition of NEt_3 (3.8 mL, 27 mmol) I_2 was added in portions until no decolorization took place. Excess of I_2 was reduced with $Na_2S_2O_5$ and methanol was partially rotary evaporated. The methanol solution was then diluted with water and brine and extracted three times with pentane. Extraction of the water phase with CH_2Cl_2 gave no further product. The product was purified further by column chromatography with hexanes/toluene (5:1); yield 2.29 g (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (br. s, 2 H), 1.99–2.02 (m, 4 H), 2.03–2.06 (m, 4 H), 3.30 (s, 3 H), 3.60 (tt, J = 3.7, 2.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 34.2, 36.3, 42.3, 56.5, 75.9 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2941, 2873, 2845, 2822, 1574, 1263, 1192, 1123, 1078, 1068, 1046, 1034 cm^{-1}. MS (EI): *m*/*z* (%) = 138 (2) [M$^+$ – N_2], 123 (4), 106 (21), 91 (60), 79 (100), 123 (4), 106 (21), 91 (60), 79 (100). $C_9H_{14}N_2O$ (166.22): calcd. C 65.03, H 8.49, N 16.85; found C 65.27, H 8.56, N 16.83. HRMS: Calcd. for $C_9H_{14}O$ (M$^+$ – N_2): 138.1045, found 138.1048.

1,2-Bis(3-*endo*-hydroxybicyclo[3.2.1]octan-8-ylidene)hydrazine (5a): 3-*endo*-Hydroxybicyclo[3.2.1]octan-8-one (**14a**) (400 mg, 2.86 mmol) and 69 mg of $N_2H_4{\cdot}H_2O$ were refluxed overnight in 15 mL of methanol. The mixture was poured into water, extracted with CH_2Cl_2, dried with $MgSO_4$ and rotary evaporated, yielding 257 mg (65%) of azine **5a** that could be recrystallized from chloroform; m.p. 218–222 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 2 H), 1.75–2.30 (m, 16 H), 2.59 (br. s, 2 H), 3.15–3.35 (m, 2 H), 4.11 (br. s, 2 H) ppm. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.54–1.72 (m, 4 H), 1.76–2.22 (m, 12 H), 2.38–2.44 (m, 2 H), 3.00–3.16 (m, 2 H), 3.87 (br. s, 2 H), 4.50 (d, J = 2.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 24.4, 24.6, 25.0, 25.1, 33.3, 33.4, 39.3, 41.9, 42.2, 44.1, 44.3, 63.67, 63.70, 177.4, 178.4 ppm. MS: *m*/*z* (%) = 76 (32) [M$^+$], 258 (3), 232 (26), 214 (4), 188 (8), 138 (93), 121 (14), 120 (13), 92 (60), 91 (100), 79 (20), 55 (21). HRMS: Calcd. for $C_{16}H_{24}N_2O_2$: 276.1838, Found: 276.1835.

1,2-Bis(3-*endo*-methoxybicyclo[3.2.1]octan-8-ylidene)hydrazine (5b): 3-*endo*-Methoxybicyclo[3.2.1]octan-8-one (**14b**) (500 mg, 3.24 mmol) and 89 mg of $N_2H_4{\cdot}H_2O$ were refluxed overnight in 10 mL of methanol. The mixture was rotary evaporated, yielding 493 mg (100%) of azine **5b**; m.p. 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$):

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δ = 1.66–2.10 (m, 12 H), 2.12–2.21 (m, 2 H), 2.26–2.33 (m, 2 H), 2.52–2.57 (m, 2 H), 3.10–3.28 (m, 2 H), 3.28 (s, 6 H), 3.40–3.46 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 24.9, 25.3, 25.4, 33.7, 33.8, 38.6, 38.9, 40.0, 40.5, 40.6, 56.5, 75.40, 75.43, 178.2, 179.1 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2939, 2873, 2821, 1677, 1442, 1436, 1425, 1278, 1199, 1116, 1077, 1068, 1040 cm^{-1}. MS: *m*/*z* (%) = 304 (43) [M$^+$], 289 (6), 273 (4), 272 (3), 246 (54), 231 (6), 214 (6), 188 (19), 152 (100), 120 (31), 93 (37), 79 (19), 58 (20). $C_{18}H_{28}N_2O_2$ (304.43): calcd. C 71.02, H 9.27, N 9.20; found C 71.14, H 9.41, N 9.22. HRMS: Calcd. for $C_{18}H_{28}N_2O_2$: 304.2151, Found: 304.2146.

***rac*-(1*R*,3*S*)-Bicyclo[3.3.0]oct-5-en-3-ol (6a):**[19] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (ddd, *J* = 12.4, 9.7, 7.0 Hz, 1 H), 1.22–1.28 (m, 1 H), 1.39–1.51 (m, 1 H), 2.08–2.18 (m, 2 H), 2.31 (qui, *J* = 6.6 Hz, 1 H), 2.42–2.62 (m, 3 H), 2.76–2.87 (m, 1 H), 4.52 (qui, *J* = 6.4 Hz, 1 H), 5.38 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.0, 35.2, 36.6, 42.2, 49.2, 76.5, 119.9, 150.3 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3611, 3053, 2955, 2935, 2891, 2850, 1429, 1322, 1249, 1236, 1203, 1148, 1121, 1048 cm^{-1}. MS: *m*/*z* (%) = 124 (20) [M$^+$], 109 (3), 106 (8), 95 (12), 91 (14), 80 (100), 67 (11). HRMS: Calcd. for $C_8H_{12}O$: 124.0888, found 124.0890.

***rac*-(1*R*,3*S*)-3-Methoxybicyclo[3.3.0]oct-5-ene (6b):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (ddd, *J* = 11.6, 10.9, 7.8 Hz, 1 H), 1.39–1.49 (m, 1 H), 2.12–2.22 (m, 2 H), 2.27–2.33 (m, 1 H), 2.42–2.56 (m, 3 H), 2.73–2.82 (m, 1 H), 3.31 (s, 3 H), 4.08 (br. qui, *J* = 6.8 Hz, 1 H), 5.30–5.33 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4, 32.4, 36.8, 39.0, 49.1, 56.8, 85.3, 119.1, 149.9 ppm.

***endo*-Tricyclo[3.3.0.0^{2,8}]octan-3-ol (7a):**[18] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (dd, *J* = 14.2, 0.9 Hz, 1 H), 1.47–1.62 (m, 3 H), 1.90–2.04 (m, 2 H), 2.08 (q, *J* = 6.1 Hz, 1 H), 2.17–2.25 (m, 1 H), 2.29–2.36 (dtd, *J* = 14.2, 9.2, 1.0 Hz, 1 H), 2.62 (q, *J* = 6.5 Hz, 1 H), 4.84 (qui, *J* = 4.2 Hz, 1 H, H_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 28.0, 34.1, 34.8, 40.9, 43.0, 47.0, 76.7 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3617, 3453, 3029, 2938, 2879, 2863, 1438, 1406, 1339, 1316, 1207, 1064, 1025 cm^{-1}. MS: *m*/*z* (%) = 124 (3) [M$^+$], 109 (3), 106 (86), 95 (14), 91 (70), 79 (56), 67 (100). HRMS: Calcd. for $C_8H_{12}O$: 124.0888, found 124.0891.

3-*endo*-Methoxytricyclo[3.3.0.0^{2,8}]octane (7b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 13.9 Hz, 1 H, H^4_{endo}), 1.48–1.57 (m, 3 H, H^2 + H^6_{endo} + H^8), 1.80–1.89 (m, 1 H, H^7_{exo}), 1.91–2.02 (m, 1 H, H^6_{exo}), 2.09 (q, *J* = 6.1 Hz, 1 H, H^1), 2.20–2.25 (m, 1 H, H^7_{endo}), 2.29–2.36 (m, 1 H, H^4_{exo}), 2.62 (q, *J* = 6.7 Hz, 1 H, H_5), 3.32 (s, 3 H, H_{Me}), 4.34 (dd, *J* = 9.3, 4.3 Hz, 1 H, H_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2 (C^7), 28.5 (C^2), 30.3 (C^8), 34.2 (C^1), 40.6 (C^6), 42.4 (C^5), 44.7 (C^4), 56.5 (C_{Me}), 85.3 (C^3) ppm. MS: *m*/*z* (%) = 138 (5) [M$^+$], 106 (95), 91 (91), 85 (93), 84 (100), 78 (84), 72 (76), 67 (82). HRMS: Calcd. for $C_9H_{14}O$: 138.1045, found 138.1043.

***endo*-Spiro[bicyclo[3.2.1]octane-8,2′-[1,3]dioxolane]-3-ol (13a):**[23,24] $Hg(OAc)_2$ (25.0 g, 78.5 mmol) was dissolved in 80 mL of H_2O. To this solution, 80 mL of THF were added and afterwards bicyclo[3.2.1]oct-2-en-8-one ethylene ketal (12) (13.03 g, 78.5 mmol). The yellow color disappeared after complete addition. After stirring for 1 h in a water bath at room temperature, 80 mL of 3 M NaOH was added followed by 80 mL of a solution of sodium borohydride (1.484 g, 39.25 mmol) in 3 M NaOH. The mixture was allowed to react for 1 h and the settled mercury was decanted. The water phase was saturated with NaCl, extracted with CH_2Cl_2, dried with $MgSO_4$ and rotary evaporated affording a crude product that was contaminated with unreacted alkene. Crystallization from Et_2O furnished 11.01 g (59.8 mmol, 76%) of alcohol **13a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 2.8 Hz, 1 H), 1.75 (d, *J* = 13.6 Hz, 2 H), 1.81–1.87 (m, 4 H), 1.91–1.96 (m, 2 H), 2.22 (dd, *J* = 15, 5 Hz, 2 H), 3.92–3.97 (m, 4 H), 4.03 (tdt, *J* = 5, 2.8, 1.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 38.27, 38.34, 63.7, 64.7, 65.3, 116.5 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3604, 2945, 2880, 2849, 1367, 1346, 1013, 947, 893 cm^{-1}. MS: *m*/*z* (%) = 184 (25) [M$^+$], 167 (7), 113 (100), 99 (78), 96 (57), 89 (52), 55 (38). HRMS: Calcd. for $C_{10}H_{16}O_3$: 184.1099, found 184.1103.

3-*endo*-Methoxybicyclo[3.2.1]octan-8-one Ethylene Ketal (13b): 3-*endo*-Hydroxybicyclo[3.2.1]octan-8-one ethylene ketal (**13a**) (17 g, 92.4 mmol) was dissolved in dry diethyl ether and added dropwise to a suspension of 37 g (924 mmol) of 60% NaH (freshly washed with hexanes) in dry ether. Then, dimethyl sulfate (26.4 mL, 35.0 g, 277 mmol) was added dropwise. After completion, the mixture was stirred for 1 h at room temperature and then refluxed overnight. The excess of NaH was destroyed by adding 50 mL of MeOH dropwise to the mixture which then was poured into a saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, dried with $MgSO_4$, rotary evaporated, and distilled (b.p. 75–76 °C, 1 Torr), yielding 15.34 g (77.5 mmol, 84%) of methyl ether **13b** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72–1.85 (m, 6 H), 1.92 (br. d, *J* = 14.8 Hz, 2 H), 2.03 (br. d, *J* = 14.8 Hz, 2 H), 3.25 (s, 3 H), 3.35 (br. t, *J* = 5.2 Hz, 1 H), 3.91–3.94 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9, 33.9, 38.3, 56.1, 63.7, 64.7, 74.7, 116.9 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2941, 2882, 2822, 1440, 1425, 1342, 1226, 1211, 1189, 1166, 1153, 1120, 1075, 1059, 1022, 1007 cm^{-1}. MS: *m*/*z* (%) = 198 (79) [M$^+$], 183 (20), 167 (32), 139 (21), 113 (66), 103 (100), 99 (100), 55 (69). $C_{11}H_{18}O_3$ (198.26): calcd. C 66.64, H 9.15; found C 66.58, H 9.21. HRMS: Calcd. for $C_{11}H_{18}O_3$: 198.1256, found 198.1250.

3-*endo*-Hydroxybicyclo[3.2.1]octan-8-one (14a):[23] Ketal **13a** (34.33 g, 186.6 mmol) was dissolved in 160 mL of acetone and 160 mL of H_2O. Then 20 mL of 1 N HCl were added. After refluxing for 3 h, the reaction mixture was neutralized with $NaHCO_3$. The weakly basic solution was extracted twice with CH_2Cl_2, the organic layer was dried with magnesium sulfate, suction-filtered through a sintered funnel and rotary evaporated. The crude product was then recrystallized from Et_2O/hexanes. The remaining mother liquor was chromatographed with hexanes/ethyl acetate (65:35); yield 18.23 g (130 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (br. s, 1 H), 1.92–1.97 (m, 2 H), 2.20–2.28 (m, 4 H), 2.32–2.39 (m, 4 H), 4.12 (t, *J* = 4.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7, 43.7, 45.1, 65.4, 222.5 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3612, 2944, 2922, 2883, 1741, 1196, 1077, 1050, 1026 cm^{-1}. MS: *m*/*z* (%) = 140 (16) [M$^+$], 122 (5), 111 (11), 95 (40), 79 (63), 71 (75), 68 (77), 57 (71), 55 (100). HRMS: Calcd. for $C_8H_{12}O_2$: 140.0837, found 140.0835.

3-*endo*-Methoxybicyclo[3.2.1]octan-8-one (14b): Ketal **13b** (14.9 g, 75.2 mmol) was dissolved in 72 mL of acetone, and 72 mL of H_2O and 8.5 mL of 1 N HCl were added. After 2 h of refluxing, the acetone was partially evaporated and the reaction mixture was neutralized with $NaHCO_3$. The weakly basic solution was extracted twice with CH_2Cl_2, the organic layer was dried with magnesium sulfate, suction-filtered through a sintered glass funnel and rotary evaporated. The crude product was then distilled (b.p. 45–46 °C, 0.8 Torr), yielding 8.374 g (54.4 mmol, 72%) ketone as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 (m, 2 H), 2.12–2.21 (m, 6 H), 2.38 (br. d, *J* = 12.9 Hz, 2 H), 3.31 (s, 3 H), 3.42 (tt, *J* = 5.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 41.0, 43.7, 56.5, 74.6, 222.7 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2940, 2876, 2822, 1731, 1712, 1438, 1427, 1278, 1247, 1201, 1154, 1115, 1071, 1042, 1030 cm^{-1}. MS: *m*/*z* (%) = 154 (100) [M$^+$], 139 (4), 126 (18), 122 (40), 111 (13), 94 (45), 79 (46), 71 (41), 55 (62). HRMS: Calcd. for $C_9H_{14}O_2$: 154.0994, found 154.0992.

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3-*endo*-Hydroxybicyclo[3.2.1]octan-8-one Dimethyl Ketal (16a): Ketone **14a** (500 mg, 3.57 mmol) was stirred at 60 °C in 20 mL of dry MeOH with trimethyl formate (0.468 mL, 4.2 mmol, 454 mg) and 14 mg of *p*TsOH for 1 h. Then 10 mL of the solution were distilled from a Vigreux column. Na_2CO_3 and brine were added and the reaction mixture was extracted with CH_2Cl_2, dried with $MgSO_4$, rotary evaporated, and recrystallized from hexanes; yield 574 mg (3.09 mmol, 86%); m.p. 61–61.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 1 H), 1.65–1.80 (m, 4 H), 1.86–1.92 (m, 2 H), 2.05–2.15 (m, 4 H), 3.19 (s, 3 H), 3.22 (s, 3 H), 4.03 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 36.2, 37.3, 47.5, 49.7, 65.7, 109.0 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3613, 2944, 2889, 2833, 1443, 1427, 1365, 1339, 1256, 1246, 1223, 1194, 1180, 1120, 1063, 1047, 1027, 1008 cm^{-1}. MS: *m*/*z* (%) = 186 (100) [M$^+$], 169 (3), 155 (9), 143 (3), 137 (3), 127 (7), 115 (38), 101 (100), 91 (72), 55 (93). $C_{10}H_{18}O_3$ (186.25): calcd. C 64.49, H 9.74; found C 64.57, H 9.96. HRMS: Calcd. for $C_{10}H_{18}O_3$: 186.1256, found 186.1251.

3-*endo*-Methoxybicyclo[3.2.1]octan-8-one Dimethyl Acetal (16b): Ketone **14b** (500 mg, 3.24 mmol) was stirred at 60 °C in 20 mL of dry MeOH with trimethyl formate (0.426 mL, 3.89 mmol, 413 mg) and 12 mg of *p*TsOH for 1 h. Then 10 mL of the solution was distilled from a Vigreux column. Na_2CO_3 and brine were added and the reaction mixture was extracted with CH_2Cl_2, dried with $MgSO_4$ and rotary evaporated. The turnover was quantitative according to GC; yield 418 mg (2.09 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.6–1.9 (m, 8 H), 2.05 (qui, *J* = 3.5 Hz, 2 H), 3.14 (s, 3 H), 3.19 (s, 3 H), 3.22 (s, 3 H), 3.33 (tt, *J* = 4.8, 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 32.8, 36.2, 47.4, 49.6, 56.1, 75.0, 109.4 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3000, 2938, 2872, 2831, 1434, 1424, 1338, 1248, 1240, 1226, 1193, 1152, 1126, 1049, 1029 cm^{-1}. MS: *m*/*z* (%) = 200 (93) [M$^+$], 185 (18), 169 (80), 153 (8), 137 (18), 115 (27), 105 (59), 101 (100), 93 (30), 55 (29). HRMS: Calcd. for $C_{11}H_{20}O_3$: 200.1412, found 200.1417.

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[1] a) *Photochemistry in Organized and Constrained Media* (Ed.: V. Ramamurthy), Wiley, New York, **1991**; b) *Artificial Enzymes* (Ed.: R. Breslow), Wiley, New York, **2005**; c) For Binding Mechanisms in Supramolecular Complexes, see H.-J. Schneider, *Angew. Chem. Int. Ed.* **2009**, *48*, 3924–3977; d) For Functional Molecular Flasks, see: M. Yoshizawa, J. K. Klosterman, M. Fujita, *Angew. Chem. Int. Ed.* **2009**, *48*, 3418–3438; e) For chirogenesis, see G. A. Hembury, V. V. Borovkov, Y. Inoue, *Chem. Rev.* **2008**, *108*, 1–73.

[2] a) K. B. Yoon, *Chem. Rev.* **1993**, *93*, 321–339; b) H. Garcia, H. D. Roth, *Chem. Rev.* **2002**, *102*, 3947–4008, and references cited therein.

[3] a) K. Takahashi, *Chem. Rev.* **1998**, *98*, 2013–2034; b) R. Breslow, S. D. Dong, *Chem. Rev.* **1998**, *98*, 1997–2012; c) D. M. Vriezema, M. Comellas-Aragones, J. A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan, R. J. M. Nolte, *Chem. Rev.* **2005**, *105*, 1445–1490.

[4] a) U. H. Brinker, M. G. Rosenberg, in: *Advances in Carbene Chemistry*, vol. 2 (Ed.: U. H. Brinker), JAI Press, Stamford, CT, **1998**, pp. 29–41; b) M. G. Rosenberg, U. H. Brinker, in: *Adv. Phys. Org. Chem.*, vol. 40 (Ed.: J. P. Richard), Academic Press, New York, **2005**, pp. 1–47; c) M. G. Rosenberg, U. H. Brinker, *Eur. J. Org. Chem.* **2006**, 5423–5440.

[5] a) R. Warmuth, J. Yoon, *Acc. Chem. Res.* **2001**, *34*, 95–105; b) P. Roach, R. Warmuth, *Angew. Chem. Int. Ed.* **2003**, *42*, 3039–3042; c) X. Liu, G. Chu, R. A. Moss, R. R. Sauers, R. Warmuth, *Angew. Chem. Int. Ed.* **2005**, *44*, 1994–1997.

[6] M. Jones Jr., *Sci. Am.* **1976**, *234*, 101–113.

[7] J.-L. Mieusset, U. H. Brinker, *J. Org. Chem.* **2008**, *73*, 1553–1558.

[8] J.-L. Mieusset, A. Schrems, M. Abraham, V. B. Arion, U. H. Brinker, *Tetrahedron* **2009**, *65*, 765–770.

[9] a) U. H. Brinker, G. Lin, L. Xu, W. B. Smith, J.-L. Mieusset, *J. Org. Chem.* **2007**, *72*, 8434–8451; b) J.-L. Mieusset, U. H. Brinker, *J. Org. Chem.* **2007**, *72*, 10211–10219.

[10] L. Trembleau Jr., J. Rebek, *Science* **2003**, *301*, 1219–1220.

[11] The chiral column used produced two baseline separated peaks only for the enantiomers of **7a** but not for those of **6** and **7b**.

[12] G. N. Fickes, C. B. Rose, *J. Org. Chem.* **1972**, *37*, 2898–2899.

[13] M. T. H. Liu, Y.-K. Choe, M. Kimura, K. Kobayashi, S. Nagase, T. Wakahara, Y. Niino, M. O. Ishitsuka, Y. Maeda, T. Akasaka, *J. Org. Chem.* **2003**, *68*, 7471–7478.

[14] a) W. Chidester, D. A. Modarelli, W. R. White III, D. E. Whitt, M. S. Platz, *J. Phys. Org. Chem.* **1994**, *7*, 24–27; b) R. Bonneau, M. T. H. Liu, in: *Advances in Carbene Chemistry*, vol. 2 (Ed.: U. H. Brinker), JAI Press, Stamford, CT, **1998**, pp. 1–28; c) X. Fu, R. A. Moss, P. Piotrowiak, M. Myahkostupov, I. R. Gould, *Org. Lett.* **2006**, *8*, 4807–4809.

[15] R. Bonneau, M. T. H. Liu, *J. Am. Chem. Soc.* **1996**, *118*, 7229–7230.

[16] J.-L. Mieusset, U. H. Brinker, *Eur. J. Org. Chem.* **2008**, 3363–3368.

[17] a) J.-L. Mieusset, U. H. Brinker, *Chem. Listy* **2004**, *98*, s50; b) J.-L. Mieusset, D. Krois, M. Pacar, L. Brecker, G. Giester, U. H. Brinker, *Org. Lett.* **2004**, *6*, 1967–1970.

[18] a) U. H. Brinker, R. Buchkremer, M. Kolodziejczyk, R. Kupfer, M. Rosenberg, M. D. Poliks, M. Orlando, M. L. Gross, *Angew. Chem.* **1993**, *105*, 1427–1429; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1344–1346; b) D. Krois, M. M. Bobek, A. Werner, H. Kählig, U. H. Brinker, *Org. Lett.* **2000**, *2*, 315–318; c) D. Krois, L. Brecker, A. Werner, U. H. Brinker, *Adv. Synth. Catal.* **2004**, *346*, 1367–1374.

[19] R. G. Buckeridge, K. J. Frayne, B. L. Johnson, *Aust. J. Chem.* **1974**, *27*, 1235–1244.

[20] J. Kossanyi, P. Jost, B. Furth, G. Daccord, P. Chaquin, *J. Chem. Res.* **1980**, *11*, 368–369.

[21] G. V. Shustov, M. T. H. Liu, K. N. Houk, *Can. J. Chem.* **1999**, *77*, 540–549.

[22] C. S. Foote, R. B. Woodward, *Tetrahedron* **1964**, *20*, 687–715.

[23] H. C. Brown, P. J. Geoghegan, *J. Org. Chem.* **1970**, *35*, 1844–1850.

[24] M. Povárny, P. Scheiber, G. Kraiss, K. Nádor, *Tetrahedron Lett.* **1984**, *25*, 1311–1312.

[25] Y. Zhang, G. B. Schuster, *J. Org. Chem.* **1995**, *60*, 7192–7197.

[26] a) H. Stetter, K.-D. Rämsch, K. Elfert, *Justus Liebigs Ann. Chem.* **1974**, 1322–1327; b) T. Momose, O. Muraoka, *Chem. Pharm. Bull.* **1978**, *26*, 2217–2223; c) T. Momose, O. Muraoka, S. Atarashi, T. Horita, *Chem. Pharm. Bull.* **1979**, *27*, 222–229.

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