A Straightforward Route to Stereodefined Functionalized Cycloheptanols and Cyclooctanols

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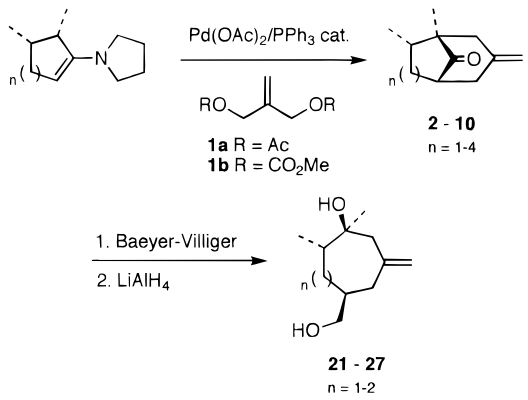
Seven-membered carbocyclic rings are structural units and subunits of biologically important natural products.[1] Although an increasing number of new methodologies have been developed,[2] the most effective strategy to these cyclic frameworks involves a ring expansion of suitable cyclic precursors.[3] Among others bicyclo[3.2.1]octan-8-ones are valuable intermediates for the synthesis of natural compounds and are good candidates to generate functionalized cycloheptanes or cycloheptenes through selective fragmentation or cleavage of bridgehead C−C bonds.[4]

Recently, we reported an easy route to functionalized methylenecycloheptanes or cycloheptanones involving a retro-Claisen condensation of β-diketones that are readily available through a palladium-catalyzed bicycloannulation of monoalkylated 1,3-diones.[5] In connection with studies on transition-metal-catalyzed cyclizations toward natural product targets, we report hereafter a straightforward route to functionalized cycloheptanols from cyclopentanones. The key reactions involve a Pd-catalyzed bicycloannulation and a two-carbon-atom ring expansion sequence based on Baeyer−Villiger (BV) oxidation followed by reductive lactone opening (Scheme 1).

Scheme 1



Several methods are available for the preparation of the requisite bicycloalkanones,but the most direct approach consists of the α,α'-annulation[6b] of a cycloalkanone via the corresponding enamine with bis-electrophilic reagents.[6] Enamines can be used as nucleophiles in π-allylpalladium chemistry,[7] and an interesting bicycloannulation of cyclic ketones with allylic bisacetate **1a** was reported by Lu in 1988.[8] The reaction involves a sequential inter- and intramolecular *C*,*C*-dialkylation and affords bicyclo[3.*n*.1]alkanones (n = 3, 2) in fairly good yields. We choose Lu's annulation as a starting point for the preparation of polycyclic ketones **2**−**10** (Table 1). With diacetate **1a** or dicarbonate **1b** it is possible to expand considerably the scope of this bicycloannulation. In most cases, biscarbonate **1b** reacts at lower temperatures compared to bisacetate **1a**. At the same time the yields increase significantly. For instance, 1-pyrrolidinocyclopentene and diacetate **1a** in the presence of Pd(OAc)$_2$ (4 mol %) and PPh$_3$ (20 mol %) in benzene (65 °C, 3 h) led to 3-methylenebicyclo[3.2.1]octan-8-one (**2**) in 63% yield.[8] Switching from diacetate **1a** to dicarbonate **1b** and performing the reaction in acetonitrile (40 °C, 20

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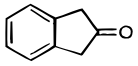
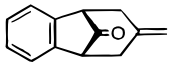
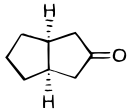
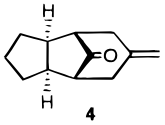
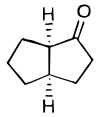
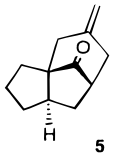
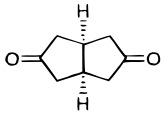
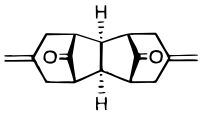
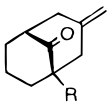
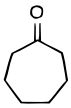
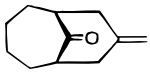
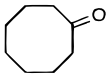
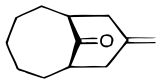
Table 1. Palladium-Catalyzed Annulation of 1-Pyrrolidinocycloalkenes[a]

Entry	Ketone or dione precursor	Reaction conditions[b] **1**, T (°C), t (h)	Product (Yield%)[c]
1		**1b**, 40, 0.3	 **2** (77)
2		**1a**, 55, 1	 (54)
3		**1b**, 45, 1	(61)
			3
4		**1a**, 65, 4	 (44)
5		**1b**, 50, 1.5	(66)
			4
6		**1a**, 65, 12	 (65)
7		**1b**, 65, 12	(67)
			5
9		**1a**,[d] 60, 1	 (44)
10		**1b**,[d] 50, 1	(47)
		1a,[e,f] 75, 1.5	(59)
			6
11		R = H { **1a**, 80, 0.3	 **7** R = H { 68
12		**1b**, 45, 1.75	80
13		R = Me { **1a**, 80, 0.3	**8** R = Me { 70
14		**1b**, 40, 3	65
15		**1a**, 45, 1	 (60)
16		**1b**, 40, 1	(59)
			9
17		**1a**, 80, 4	 (26)
18		**1b**, 45, 4.5	(31)
19		**1a**, 80, 4[e]	(44)
			10

[a] See ref 19. [b] $Pd(OAc)_2/PPh_3$ (4/20 mol %), MeCN. [c] Yields of isolated products after purification by flash chromatography. [d] **1a** (2.2 equiv). [e] Addition of **1a** with a syringe pump. [f] **1a** (4.7 equiv).

min), we could improve substantially the yield (77%) of **2**.[9] It turns out that the choice of solvent is crucial for the annulation. The yields were unsatisfactory in dioxane or MeOH (30−35%). On the other hand, with acetonitrile the reaction time was shortened. Indeed, satisfactory yields are obtained when the reaction time is carefully controlled, presumably, by avoiding partial product degradation, since longer reaction times (5 h) resulted in considerable lower yield (33%). We extended the reaction to bicyclic ketones, keeping in mind that the products could be useful for the basic framework of terpenes (Table 1, entries 4−7). For instance, *cis*-bicyclo[3.3.0]octan-3-one afforded ketone **4** in 66% yield (Table 1, entry 5) featuring the tricyclo[5.3.1.$0^{2,6}$]undecane structure of the sesquiterpene alcohol apollan-11-ol.[10] Similarly, 9-methylenetricyclo[5.3.1.$0^{1,5}$]undecan-11-one (**5**), the basic structure of cedrol,[11] was obtained in 67% yield from the enamine of *cis*-bicyclo[3.3.0]octan-2-one (Table 1, entries 6, 7). As expected, the conformationally restricted shape of these bicyclic systems allows high stereocontrol upon formation of tricyclic ketones **4** and **5**. It is worth noting that formation of the six-membered ring in **5** also gives rise to a new stereogenic quaternary angular center.

(9) Among other phosphine ligands examined, trifurylphosphine (20 mol %) and dppb (10 mol %) proved also effective.

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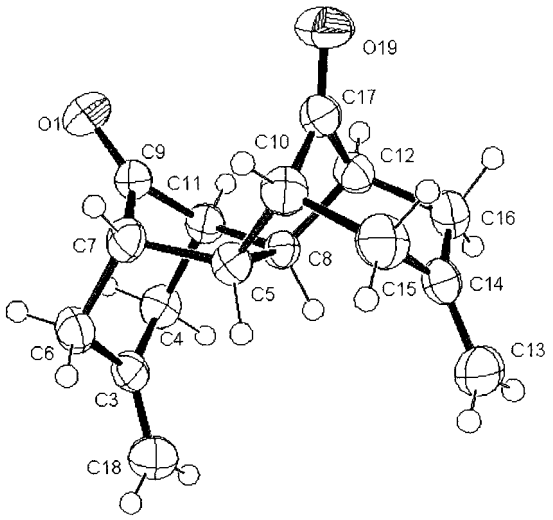


Figure 1. X-ray crystal structure of dione **6**.

Under similar conditions, the annulation of pyrrolidine dienamine derived from *cis*-bicyclo[3.3.0]octan-3,7-dione[12] with 2.2 equiv of **1a** leads to the tetracyclic dione **6** as a single diastereomer (Table 1, entry 8). The yield was significantly improved when **1a** was slowly added by using a syringe pump (Table 1, entry 10). Considering the rigid conformation of the dienamine precursor,[12] it is reasonable to state that the bis-bicycloannulation had occurred at the *exo* face *syn* with respect the hydrogen atoms at the ring fusion. The stereochemical assignment of this diketone was straightforward since examination of the ^{13}C NMR spectrum of the crude reaction mixture reveals only six new resonances consistent with a structure that has C_2 symmetry. The fine structure of **6** was confirmed by a single-crystal X-ray diffraction analysis (Figure 1).[13] However, attempts to isolate a monoannulated product from *cis*-bicyclo[3.3.0]octan-3,7-dione were unsuccessful. For instance, even when the reaction was carried out with 1 equiv of **1a** (or **1b**), **6** was the sole product formed. For future prospects to higher analogues, bicycloannulation of six- to eight-membered cycloalkanones was briefly examined (Table 1, entries 11−19). The bicycloalkanones **7**−**10** were obtained in yields that decreased when the ring size increased. Most noteworthy the bicyclo[5.3.1]undecane framework, the basic AB ring system of taxoids, was obtained in a single step (44%) from 1-pyrrolidinocyclooctene and **1b** (Table 1, entry 19). The *cis* stereochemistry of **10** was easily deduced from the ^{13}C NMR spectrum, which presents eight lines.[14]

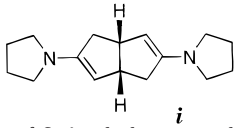
The bridge fission of bicyclic alkanones to cycloheptanols or hydroazulane systems was performed in a straightforward fashion combining BV oxidation of the ketones and subsequent reduction of the resulting lactones with $LiAlH_4$ (Table 2). As expected, BV oxidation[15] of bicyclic ketones **2**−**5** with peracetic acid in the presence

Table 2. Baeyer−Villiger Oxidation and Subsequent Reductive Ring Opening of Ketones 2−10

Entry	Ketone	Oxidation product,[a] Yield (%)	Reduction product,[b] Yield (%)
1	**2**	**11** (99)	**21** (87)
2	**3**	**12** (92)	**22** (78)
3	**4**	**13** (81)	**23** (80)
4	**5**	**14**[c] (75)	**24** (94)
5	**6**	**15** (89)	**25**[d] (83)
6	**7**	**16** R = H (90)	**26** R = H (68)
7	**8**	**17** R = Me (85)	**27** R = Me (85)
8	**9**	**18** (6)[e] **19** (54)[e]	
9	**10**	**20** (65)[f]	

[a] AcOOH (1.1 equiv), Na_2CO_3 (1.3 equiv), 0 °C, 1−2 h. [b] $LiAlH_4$ (2 equiv), rt, 2 h. [c] Contaminated with 10% of regioisomer. [d] **25** obtained as a single diastereomer. Configuration of bridged carbon atom is tentative (see text). [e] 0 °C to rt, 18 h; yields based on recovered starting material (brsm), 47% conversion of **9**. [f] 0 °C to rt, 2.5 days; yield brsm, 85% conversion of **10**.

(12) Pyrrolidine dienamine ***i*** derived from *cis*-bicyclo[3.3.0]octan-3,7-dione is a stable reddish crystalline compound and was obtained as a single regioisomer (6 lines in the ^{13}C NMR spectrum). For related dienamines, see: Askani, R.; Littmann, M. *Tetrahedron Lett.* **1985**, *26*, 5519.



i

(13) X-ray structure of **6**. A colorless crystal (0.4 × 0.4 × 0.3 mm) obtained from petroleum ether and ethyl acetate was used for data collection. $C_6H_{12}O_6$, $M_r = 180.16$, orthorhombic, space group $P2_12_12_1$, $a = 10.3602(4)$ Å, $b = 10.7371(4)$ Å, $c = 11.3950(4)$ Å, $\alpha = 90.00(1)°$, $\beta = 90.00(1)°$, $\gamma = 90.00(1)°$, $V = 1267.6(1)$ Å^3, $d_{calcd} = 1.25$ g cm^{-3}. All the measurements were made on a Rigaku diffractometer with Mo Kα radiation. Cell constants and the orientation matrix for data collection were obtained from a least-squares refinement using setting angles of 30 reflections in the range $\theta = 1-25°$ for $Z = 6$. A total of 1495 reflections were collected at $T = 298$ K and $R = 0.035$ for the refined structure. The final atomic coordinates and full list of bond lengths and angles for dione **6** have been deposited with the Cambridge Crystallographic Data Centre. The deposit number allocated to the crystal structure of **6** is CCDC 142913.

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of Na_2CO_3 occurred smoothly, and the corresponding lactones **11**−**14** were obtained in excellent yields (75−99%). Oxidation of unsymmetrical ketone **5** resulted in the formation of a 10:1 mixture of regioisomeric lactones (75%). The major isomer **14** was assigned by NMR analyses. On exposure to peracetic acid, the tetracyclic diketone **6** gave a single monolactone **15** even in the presence of an excess of the reagent (Table 2, entry 9).[16] Reductive lactone ring opening was performed at room temperature using $LiAlH_4$ (2 equiv) in ether, affording 3-methylene-*cis*-5-hydroxymethylcycloheptanols **21**−**24** in good yields as single diastereomers. Concomitant reduction of the ketone and the lactone bridge of **15** afforded triol **25**. The stereochemistry of the carbinol at the methylene bridge was tentatively assigned as depicted. We assume a hydride delivery to the more accessible face of the carbonyl in the 4-*exo*-methylenecyclohexanone subunit, which is blocked in the chair conformation. Thus, functionalized 5,7-**23**−**24** and 6,7-fused bicyclic system **22** and even the more complex tricyclic triol **25** are now easily available with complete stereocontrol of up to five stereocenters. The formation of *trans*-bicyclo[5.3.0]decane **24** (5,7-fused) featuring a stereogenic angular carbinol center is worth noting and may serve as a model for a strategy to dactylol,[17] a sesquiterpene alcohol with a *trans*-5,8-fused system. As an extension of this study, bicyclo[3.3.1]nonanones **7** and **8** were converted to cyclooctanols **26** and **27** in good overall yields[18] (Table 2, entries 6, 7). Unlike the unsymmetrical ketone **5** (vide supra), BV oxidation of **8** gave the expected bicyclic lactone **17** as a single regioisomer. With the less constrained bicyclo[4.3.1]decanone **9** compared to ketones **2**−**8**, epoxidation of the *exo*-methylene competes favorably with BV oxidation, and stereoselective formation of ketoepoxide **19** as the major product (54%) was observed along with lactone **18** in only 6% yield. It was not surprising to observe the same trends for **10**, which exclusively forms ketoepoxide **20**, which resists further oxidation even in the presence of an excess of oxidant.

In summary, we have developed a straightforward and diastereoselective four-step sequence to convert cyclopentanones into functionalized cycloheptanols in synthetically useful overall yields. In an exploratory study it was also shown that cyclooctanols are available from cyclohexanones. The transformation is of general applicability and combines a palladium-catalyzed bicycloannulation of cycloalkanones with Baeyer−Villiger oxidation, and the reductive ring opening of bi- and polycyclic lactones. The bicycloannulation was also investigated as a possible route to the polycyclic framework of sesquiterpenes such as cedrol or apollanol. This simple approach should be synthetically useful, and the ability to manipulate independently or simultaneously chemodifferentiated hydroxyl and exocyclic methylene groups should give special merits to these polycyclic building blocks.

Experimental Section

Reactions were carried out under an argon atmosphere. Acetonitrile (CaH_2) and ether (sodium benzophenone ketyl) were distilled immediately prior to use. *N*-(1-Cycloalkenyl)pyrrolidines were prepared as described by Stork[19] and distilled before use. The ketones used in the enamine syntheses were commercially available except *cis*-bicyclo[3.3.0]octan-2-one[20] and *cis*-bicyclo[3.3.0]octan-3-one,[20] which were obtained as described. Analytical thin-layer chromatography was performed on silica gel 60 F_{254} plates (0.25 mm). Flash chromatography was performed on silica gel 60 (230−400 mesh). Melting points were taken on a capillary apparatus and are uncorrected. IR spectra were recorded as liquid films or as thin disks with KBr. ^{1}H and ^{13}C NMR were recorded at 200 or 400 MHz referenced to $CDCl_3$ at δ 7.24 and 77.0, respectively. The different types of carbon in the structures have been identified by DEPT techniques.

Typical Procedure of Bicycloannulation of Cycloalkanones. Enamine (1.2 mmol) was added to a stirred solution of $Pd(OAc)_2$ (9 mg, 0.048 mmol), PPh_3 (52 mg, 0.24 mmol), and dicarbonate **1b** (204 mg, 1 mmol) [or diacetate **1a** (172 mg, 1 mmol)] in acetonitrile (5 mL). The mixture was heated for the reported time (Table 1). Water (10 mL) was added, and the mixture was stirred at 50 °C for 2 h and concentrated in vacuo. The aqueous layer was extracted with ether, and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography using ether/petroleum ether as the eluent.

3-Methylenebicyclo[3.2.1]octan-8-one (2). Flash column chromatography (PE/Et_2O, 9/1) gave **2** as a colorless oil (77%): R_f 0.51 (PE/Et_2O, 5/1); IR ν 2981, 1748, 1647, 1447, 1187, 1087 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.69−1.75 (m, 2H), 1.88−1.94 (m, 2H), 2.27 (m, 2H), 2.39−2.48 (m, 2H), 2.68−2.76 (m, 2H), 4.99 (t, J = 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.8 (t), 44.3 (d), 44.7 (t), 115.4 (t), 141.6 (s), 222.0 (s). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.43; H, 8.74.

7-Methylene-5,9-methanobenzocycloheptan-10-one (3). Flash column chromatography (PE/Et_2O, 9/1) gave **3** as a clear yellow solid (60%): mp 86 °C; R_f 0.55 (PE/Et_2O, 5/1); IR (KBr) ν 2973, 1760, 1684, 1460, 1105, 1054, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.63 (dd, J = 14.5, 2.8 Hz, 2H), 2.85 (ddd, J = 14.4, 2.8, 2.0 Hz, 2H), 3.38 (t, J = 2.8 Hz, 2H), 4.58 (t, J = 2.0 Hz, 2H), 7.23 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 43.5 (t), 51.5 (d), 116.3 (t), 122.9 (d), 127.5 (d), 139.4 (s), 139.5 (s), 216.2 (s). Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.49; H, 6.62.

6-Methylenedecahydro-4,8-methanoazulen-9-one (4). Flash column chromatography (PE/Et_2O, 9/1) gave **4** as a colorless oil (66%): R_f 0.55 (PE/Et_2O, 5/1); IR (KBr) ν 2940, 1745, 1635, 1440, 1082 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18−1.50 (m, 4H), 1.81−1.91 (m, 2H), 2.05 (t, J = 3.0 Hz, 2H), 2.31 (m, 2H), 2.48 (m, 2H), 2.64 (m, 2H), 4.90 (t, J = 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.1 (t), 33.8 (t), 42.1 (d), 44.2 (t), 52.4 (d), 114.4 (t), 142.3 (s), 222.2 (s). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. C, 81.60; H, 9.08.

5-Methyleneoctahydro-3a,7-methanoazulen-9-one (5). Flash column chromatography (PE/Et_2O, 95/5) gave **5** as a colorless oil (67%): R_f 0.67 (PE/Et_2O, 5/1); IR (KBr) ν 2982, 1745, 1640, 1440, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95−1.20 (m, 2H), 1.45−1.61 (m, 4H), 1.83−1.95 (m, 2H), 2.05−2.67 (m, 6H), 4.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.1 (t), 28.7 (t), 30.0 (t), 35.1 (t), 43.0 (d), 43.8 (t), 47.5 (d), 48.7 (t), 58.0 (s), 114.2 (t), 142.6 (s), 221.6 (s). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.64; H, 9.19.

(16) The conversion of dione **6** to ketolactone **15** was complete within 1 h. On exposure to peracetic acid for 48 h, **15** reacted sluggishly at room temperature to afford an inseparable mixture of bislactone regioisomers (<10%) as estimated by ^{13}C NMR analysis.

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Diketone 6. Flash column chromatography (PE/Et_2O, 7/3) gave **6** as a white crystalline solid (49%): mp 238−240 °C; R_f 0.22 (PE/Et_2O, 2/1); 0.44 (PE/Et_2O, 1/1); IR (KBr) ν 2944, 1750, 1633, 1444, 1088 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (m, 6H), 2.44−2.69 (m, 8H), 4.97 (t, J = 1.8 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 42.4 (d), 44.6 (t), 52.0 (d), 115.6 (t), 140.9 (s), 219.9 (s). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.37; H, 7.40.

3-Methylenebicyclo[3.3.1]nonan-9-one (7). Flash column chromatography (PE/Et_2O, 9/1) gave **7** as a colorless oil (80%): R_f 0.52 (PE/Et_2O, 5/1); IR ν 2927, 1723, 1655, 1446, 1083 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22−1.41 (m, 2H), 1.88−2.04 (m, 4H), 2.45−2.79 (m, 6H), 4.82 (t, J = 2.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.5 (t), 34.9 (t), 41.2 (t), 46.4 (d), 110.1 (t), 144.8 (s), 218.8 (s). Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.82; H, 9.28.

1-Methyl-3-methylenebicyclo[3.3.1]nonan-9-one (8). Flash column chromatography (PE/Et_2O, 9/1) gave **8** as a colorless oil (70%) after purification by column chromatography (PE/Et_2O, 9/1): R_f 0.55 (PE/Et_2O, 5/1); IR ν 2926, 1715, 1631, 1445, 1081 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.21−1.37 (m, 2H), 1.66 (ddt, J = 1.8, 5.7, 13.5 Hz, 1H), 1.89−2.02 (m, 3H), 2.39−2.71 (m, 5H), 4.79 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.6 (t), 23.7 (q), 35.4 (t), 41.5 (t), 42.9 (t), 46.6 (s), 47.0 (d), 49.1 (t), 109.9 (t), 145.5 (s), 220.2 (s). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.31; H, 9.69.

8-Methylenebicyclo[4.3.1]decan-10-one (9). Flash column chromatography (PE/Et_2O, 9/1) gave **9** as a colorless oil (60%): R_f 0.55 (PE/Et_2O, 5/1); IR ν 2927, 1707, 1634, 1447, 1125, 1083 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29−1.85 (m, 8H), 2.30 (d, J = 13.5 Hz, 2H), 2.55−2.75 (m, 4H), 4.90 (t, J = 1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 25.8 (t), 31.1 (t), 40.3 (t), 48.4 (d), 112.9 (t), 145.6 (s), 215.3 (s). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.27; H, 9.64.

***cis*-9-Methylenebicyclo[5.3.1]undecan-11-one (10).** Flash column chromatography (PE/Et_2O, 9/1) gave **10** as a colorless oil (44%): R_f 0.47 (PE/Et_2O, 5/1); IR (KBr) ν 2927, 1698, 1655, 1455, 1122 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (m, 4H), 1.77 (m, 6H), 2.21 (d, J = 12.4 Hz, 2H), 2.40−2.61 (m, 4H), 4.93 (t, J = 1.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.4 (t), 30.3 (t), 31.0 (t), 40.3 (t), 50.1 (d), 114.9 (t), 140.2 (s), 218.5 (s). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.76; H, 10.07.

General Procedure of Baeyer−Villiger Oxidation. Peracetic acid (100 μL, 32% solution in acetic acid) was added to a cooled (0 °C) solution of ketone (0.5 mmol) in CH_2Cl_2 (10 mL) containing Na_2CO_3 (70 mg, 0.7 mmol). The resulting mixture was stirred at 0 °C for 2 h, washed with saturated aqueous $NaHSO_3$, and dried (Na_2SO_4). Solvent removal followed by flash chromatography afforded the corresponding lactone.

3-Methylene-6-oxabicyclo[3.2.2]nonan-7-one (11). Flash column chromatography (PE/Et_2O, 7/3) gave **11** as a white solid (99%): mp 36−37 °C; R_f 0.47 (PE/Et_2O, 1/1); IR (KBr) ν 2952, 1739, 1651, 1444, 1073, 1037 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76−2.05 (m, 4H), 2.40−2.73 (m, 4H), 2.84 (m, 1H), 4.70 (m, 1H), 4.92 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.2 (t), 22.7 (t), 37.8 (t), 37.9 (d), 42.3 (t), 76.1 (d), 116.3 (t), 142.0 (s), 176.2 (s). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.14; H, 7.88.

10-Methylene-12-oxatricyclo[6.3.2.0^{2,7}]trideca-2(7),3,5-trien-13-one (12). Flash column chromatography (PE/Et_2O, 7/3) gave **12** as a white crystalline solid (92%): mp 107−108 °C; R_f 0.30 (PE/Et_2O, 2/1); IR (KBr) ν 2925, 1747, 1650, 1463, 1140, 1029, 909, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54−2.95 (m, 4H), 3.85 (dd, J = 6.5, 2.0 Hz, 1H), 4.62 (m, 2H), 5.44 (dd, J = 4.6, 2.3 Hz, 1H), 7.13−7.33 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 37.9 (t), 41.0 (t), 46.0 (d), 79.2 (d), 117.7 (t), 124.0 (d), 126.2 (d), 127.5 (d), 128.8 (d), 134.5 (s), 135.1 (s), 139.4 (s), 174.5 (s). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.78; H, 5.91.

(1*R,2*S**,6*R**,7*S**)-9-Methylene-11-oxatricyclo[5.3.2.0^{2,6}]-dodecan-12-one (13).** Flash column chromatography (PE/Et_2O, 8/2) gave **13** as a white crystalline solid (81%): mp 94−95 °C. R_f 0.36 (PE/Et_2O, 2/1); IR (KBr) ν 2950, 1739, 1650, 1446, 1083, 1012 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15−1.95 (m, 6H), 2.27−2.72 (m, 7H), 4.53 (dd, J = 1.7, 4.9 Hz, 1H), 4.87 (d, J = 1.2 Hz, 1H), 4.89 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.5 (t), 31.3 (t), 33.8 (t), 36.8 (t), 38.2 (d), 38.6 (d), 41.8 (t), 44.1 (d), 80.0 (d), 115.5 (t), 142.4 (s), 175.7 (s). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.78; H, 8.46.

(1*R,5*S**,7*R**)-9-Methylene-11-oxatricyclo[5.3.2.0^{1,5}]-dodecan-12-one (14).** Flash column chromatography (PE/Et_2O, 9/1) gave **14** as a colorless oil (75%, 10:1 mixture of regioisomers): R_f 0.40 (PE/Et_2O, 2/1); IR (neat) ν 2946, 1746, 1646, 1451, 1045, 938 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18−2.21 (m, 9H), 2.35−2.86 (m, 5H), 4.83 (m, 1H), 4.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0 (t), 27.7 (t), 33.3 (t), 37.0 (t), 37.5 (d), 39.5 (d), 39.7 (t), 45.8 (t), 91.6 (s), 115.7 (t), 142.0 (s), 176.2 (s). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.71; H, 8.23.

Ketolactone (15). Flash column chromatography (PE/Et_2O, 1/1) gave **15** as a white crystalline solid (89%): mp 230−232 °C; R_f 0.23 (Et_2O/PE, 2/1); IR (KBr) ν 2935, 1751, 1651, 1434, 1090, 1048 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07−2.72 (m, 13H), 4.56 (m, 1H), 4.96 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 37.4 (t), 38.9 (d), 39.6 (d), 42.1 (t), 44.5 (d), 44.9 (t), 46.7 (t), 52.1 (d), 52.9 (d), 81.0 (d), 116.1 (t), 116.7 (t), 140.2 (s), 141.3 (s), 173.8 (s), 217.7 (s). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.29; H, 6.92.

3-Methylene-9-oxabicyclo[3.3.2]decan-10-one (16). Flash column chromatography (PE/Et_2O, 2/1) gave **16** as a white solid (90%): mp 44−45 °C; R_f 0.27 (PE/Et_2O 2/1); IR (KBr) ν 2931, 1728, 1447, 1042, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (m, 1H), 1.72−2.07 (m, 4H), 2.40 (m, 2H), 2.62 (m, 2H), 2.80 (m, 1H), 3.09 (m, 1H), 4.53 (q, J = 4 Hz, 1H), 4.83 (d, J = 2 Hz, 1H), 4.87 (d, J = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.5 (t), 26.5 (t), 31.2 (t), 36.0 (t), 41.0 (t), 43.8 (d), 75.1 (d), 114.3 (t), 144.6 (s), 177.5 (s). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.18; H, 8.41.

1-Methyl-3-methylene-9-oxabicyclo[3.3.2]decan-10-one (17). Flash column chromatography (PE/Et_2O, 7/3) gave **17** as a white solid (85%): mp 60−61 °C; R_f 0.27 (PE/Et_2O, 2/1); IR (KBr) ν 2932, 1723, 1644, 1445, 1050, 992 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.49 (m, 1H), 1.69−2.03 (m, 4H), 2.27−2.75 (m, 5H), 3.09 (m, 1H), 4.81 (d, J = 1.8 Hz, 1H), 4.85 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0 (t), 26.5 (t), 32.8 (q), 36.3 (t), 38.0 (t), 43.8 (d), 47.9 (t), 81.0 (s), 114.5 (t), 144.3 (s), 176.9 (s). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.13; H, 8.87.

3-Methylene-10-oxabicyclo[4.3.2]undecan-11-one (18) and Ketoepoxide 19. Flash column chromatography (PE/Et_2O, 2/1)-furnished a 1:9 mixture of **18** and **19** (28% isolated yield; 60% based on recovered starting material): R_f 0.50 (PE/Et_2O, 1/1). **18**: Partial ^1H NMR ($CDCl_3$) δ 2.28−2.58 (m, 4H), 3.27 (m, 1H), 4.70 (m, 1H), 4.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.5 (t), 24.8 (t), 32.1 (t), 34.6 (t), 38.4 (t), 43.3 (t), 44.1 (d), 77.8 (d), 115.8 (t), 144.3 (s), 177.9 (s). **19**: White crystalline solid; mp 116−117 °C; IR (KBr) ν 2930, 1704, 1445, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17−1.95 (m, 10H), 2.35 (dd, J = 14.0, 6.6 Hz, 2H), 2.57 (m, 2H), 2.89 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 26.6 (t), 30.9 (t), 38.4 (t), 47.1 (d), 54.9 (s), 57.4 (t), 214.0 (s). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.17; H, 8.89.

Ketoepoxide 20. Flash column chromatography (PE/Et_2O, 7/3) gave **20** as a white crystalline solid (55% isolated yield; 65% brsm): mp 124−125 °C; R_f 0.58 (PE/Et_2O, 1/1); IR (KBr) ν 2920, 1698, 1442 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19−1.25 (m, 4H), 1.40 (d, J = 13.6 Hz, 2H), 1.60−1.96 (m, 6H), 2.37 (dd, J = 13.6, 5.7 Hz, 2H), 2.51 (m, 2H), 2.88 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 24.4 (t), 30.3 (t), 31.8 (t), 38.0 (t), 49.2 (d), 53.6 (s), 57.1 (t), 217.2 (s). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.97; H, 9.27.

Reduction of Lactones. $LiAlH_4$ (21 mg, 0.84 mmol) was added portionwise to a cooled (0 °C) solution of lactone (0.42 mmol) in Et_2O (5 mL). The mixture was stirred at ambient temperature for 2 h. Water (15 μL, 0.84 mmol) was carefully added, and the mixture was stirred for an additionnal hour, filtered through a short pad of Celite, and concentrated in vacuo. The residue was purified by column chromatography (AcOEt/PE) to afford the corresponding diol.

***cis*-5-Hydroxymethyl-3-methylenecycloheptanol (21).** Flash column chromatography (AcOEt/PE, 6/1) gave **21** as a colorless oil (87%): R_f 0.51 (AcOEt/PE, 10/1); IR (KBr) ν 3338, 2926, 1644, 1445, 1033, 897 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30−2.02 (m, 5H), 2.37−2.52 (m, 4H), 3.39−3.50 (m, 2H), 3.98 (m, 1H), 4.83 (m, 1H), 4.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6 (t), 36.1 (t), 38.9 (t), 40.9 (d), 42.9 (t), 67.6 (d + t), 115.6 (t), 143.6 (s). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.93; H, 10.22.

***cis*-9-Hydroxymethyl-7-methylenebenzocycloheptan-5-ol (22).** Flash column chromatography (AcOEt/PE, 2/1) gave **22** as a white crystalline solid (78%): mp 115−116 °C; R_f 0.70 (AcOEt/PE, 10/1); IR (KBr) ν 3343, 2922, 1645, 1455, 1052, 1040, 908, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (m, 1H), 2.46 (m, 2H), 2.63 (m, 2H), 3.05 (m, 1H), 3.98 (m, 2H), 4.89 (m, 3H), 7.22−

7.40 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 38.9 (t), 44.9 (t), 46.5 (d), 65.7 (t), 73.1 (d), 115.2 (t), 126.9 (d), 127.9 (d), 128.3 (d), 129.2 (d), 140.0 (s), 142.6 (s), 144.3 (s). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.33; H, 7.96.

(3a*S,4*R**,8a*R**,8*S**)-8-Hydroxymethyl-6-methylenedecahydroazulen-4-ol (23).** Flash column chromatography (AcOEt/PE, 3/1) gave **23** as a white crystalline solid (80%): mp 125−126 °C; R_f 0.64 (AcOEt/PE, 10/1); IR (KBr) ν 3333, 2944, 1645, 1455, 1069, 1019 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22−1.98 (m, 7H), 2.09 (m, 2H), 2.30−2.61 (m, 4H), 3.41 (dd, J = 7.1, 1.9 Hz, 2H), 3.96 (d, J = 10.4 Hz, 1H), 4.73 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.5 (t), 26.9 (t), 27.1 (t), 34.7 (t), 39.5 (d), 42.0 (d), 42.3 (t), 46.8 (d), 66.9 (t), 72.3 (d), 112.8 (t), 146.5 (s). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.32; H, 10.18.

(3a*R,7*R**,8a*S**)-7-Hydroxymethyl-5-methyleneoctahydroazulen-3a-ol (24).** Flash column chromatography (AcOEt/PE, 4/1) gave **24** as a colorless oil (94%): R_f 0.64 (AcOEt/PE, 10/1); IR (KBr) ν 3332, 2920, 1634, 1450, 1022, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 10H), 2.29 (d, J = 13.8 Hz, 1H), 2.34 (m, 2H), 2.57 (d, J = 13.8 Hz, 1H), 3.44 (d, J = 6.5 Hz, 2H), 4.82 (m, 1H), 4.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8 (t), 28.8 (t), 31.0 (t), 37.7 (t), 40.1 (d), 41.0 (t), 48.0 (t), 48.8 (d), 67.5 (t), 78.6 (s), 115.4 (t), 145.2 (s). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.18.

(1*R,2*S**,6*R**,7*R**,8*S**,12*R**,13*S**)-13-Hydroxy-6-hydroxymethyl-4,10-bismethylenetricyclo[5.5.1^{8,12}.0^{1,7}]cyclododecan-2-ol (25).** Flash column chromatography (AcOEt/PE, 4/1) gave **25** as a white crystalline solid (80%): mp 129−130 °C; R_f 0.51 (AcOEt/PE, 10/1); IR (KBr) ν 3294, 2922, 1645, 1435, 1090, 1023, 893 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.97−2.72 (m, 13H), 3.43−3.57 (m, 2H), 4.07 (m, 2H), 4.77 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 40.8 (d), 41.2 (t), 41.7 (t), 42.2 (t), 45.6 (t), 47.5 (d), 49.4 (d), 49.7 (d), 53.0 (d), 64.8 (t), 71.4 (d), 80.4 (d), 113.2 (t), 116.4 (t), 143.0 (s), 143.8 (s). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.57; H, 9.17.

***cis*-5-Hydroxymethyl-3-methylenecyclooctanol (26).** Flash column chromatography (AcOEt/PE, 5/1) gave **26** as a colorless oil (67%): R_f 0.51 (AcOEt/PE, 10/1); IR (KBr) ν 3390, 2920, 1638, 1445, 1017, 893 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14−2.01 (m, 7H), 2.34−2.53 (m, 4H), 3.43 (m, 2H), 3.95 (m, 1H), 4.84 (m, 1H), 4.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.0 (t), 31.0 (t), 34.4 (t), 38.6 (d), 40.0 (t), 42.1 (t), 68.5 (t), 69.7 (d), 114.4 (t), 145.1 (s). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.37; H, 10.51.

***cis*-5-Hydroxymethyl-1-methyl-3-methylenecyclooctanol (27).** Flash column chromatography (AcOEt/PE, 4/1) gave **27** as a white crystalline solid (85%): mp 97−98 °C; R_f 0.64 (AcOEt/PE, 10/1); IR (KBr) ν 3371, 2922, 1635, 1456, 1050, 890 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 1H), 1.24 (s, 3H), 1.42 (m, 1H), 1.48 (m, 1H), 1.60 (m, 1H), 1.63 (m, 1H), 1.73 (ddm, J = 14.9, 10.2 Hz, 1H), 1.92 (m, 1H), 2.02 (dd, J = 14.9, 11.9 Hz, 1H), 2.24 (d, J = 13.5 Hz, 1H), 2.32 (d, J = 13.5 Hz, 1H), 2.50 (d, J = 14.9 Hz, 1H), 3.45 (m, 2H), 4.84 (m, 1H), 4.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.1 (t), 31.3 (q), 32.1 (t), 36.4 (d), 39.4 (t), 40.4 (t), 45.7 (t), 68.7 (t), 70.5 (s), 113.6 (t), 146.5 (s). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.59; H, 11.06.

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