Stereoselective Synthesis of (1*R*,5*S*)-4-[(*E*)-Alkylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones

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Abstract: Various (1*R*,5*S*)-4-[(*E*)-alkylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones were prepared, stereoselectively, via coupling of (1*R*,5*S*)-4-[(*E*)-(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one with Grignard reagents, potassium cyanide, and 2-methyl-1*H*-indole.

Key words: Grignard reactions, chiral pool, coupling, terpenoids, enaminones

(+)-Camphor (**1**) and its derivatives, belong to the most frequently employed types of ex-chiral pool starting materials utilized as building blocks, ligands in various asymmetric reagents and/or catalysts, resolving agents, and shift reagents in NMR spectroscopy. The interest in the chemistry of camphor (**1**) and related terpenoids is associated with its availability as well as with the diversity of its transformations.[1]

2-Substituted alkyl 3-(dimethylamino)prop-2-enoates and related enaminones are a group of reagents and building blocks, which can be used as versatile reagents for the preparation of a variety of dehydroalanine derivatives, heterocyclic systems, fuctionalized heterocycles, natural products, and their analogs.[2] Recently, 3-(dimethylamino)prop-2-enoates have also found use in combinatorial synthesis.[3]

Acid-catalyzed substitution of the dimethylamino group in 3-(dimethylamino)propenoates with O-, C-, and N-nucleophiles represents a general synthetic method for β-derivatisation of α,β-unsaturated carbonyl compounds.[2,3] Since the pioneering work of Benary,[4] coupling of vinylogous amides with Grignard reagents[5] and organolithium compounds[6] has been used for the conversion of aminomethylidene compounds into the alkylidene derivatives.

Recently, our studies in the field of 3-dimethylaminopropenate chemistry were extended towards the preparation and utilization of (+)-camphor (**1**) derived enaminones. In connection with this, we reported the stereoselective synthesis of 1,2,4-triazolo[4,3–*x*]azinyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones[7] and *N*-substituted (1*R*,5*S*)-4-aminomethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones from the corresponding camphor-derived enaminones.[8]

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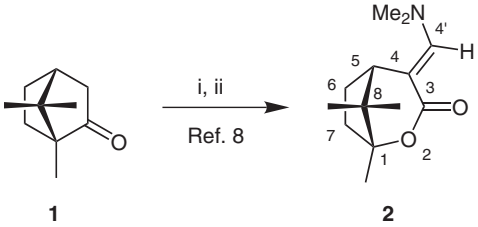
In continuation of our work in this field we now report a stereoselective synthesis of (1*R*,5*S*)-4-[(*E*)-alkylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **3**–**5** by coupling of (1*R*,5*S*)-4-[*(E)*-(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**2**) with Grignard reagents, potassium cyanide, and 2-methyl-1*H*-indole.

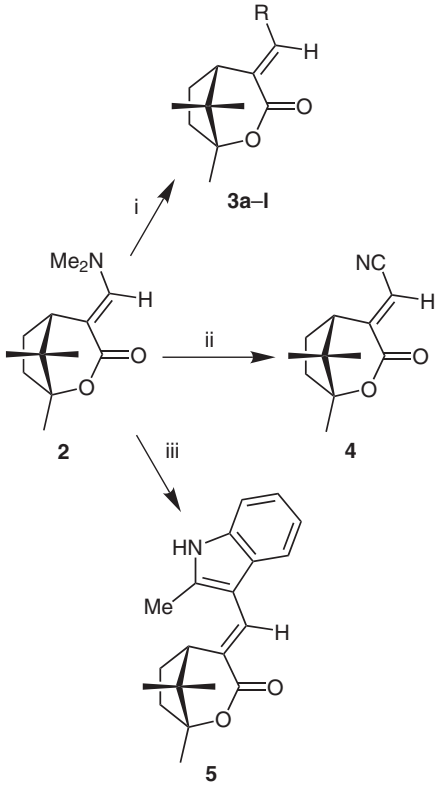
Enaminone **2** was prepared in two steps from (+)-camphor (**1**) according to literature procedures (Scheme 1).[8]



Scheme 1 (i) AcOOH, HOAc, NaOAc, r.t.; (ii) *t*-BuOCH(NMe$_2$)$_2$, decaline, reflux, chromatographic separation.[8]

Treatment of **2** with Grignard reagents in THF at –78 °C to r.t. afforded the corresponding dimethylamine substitution products **3a**–**l**. In the reactions of **2** with *n*-alkyl-, ethynyl-, benzyl-, and arylmagnesium halides, the *E*-isomers of the substitution products **3a**,**b**,**d**,**h**–**l** were obtained, stereoselectively, in 21–83% yields. However, treatment of **2** with *i*-propyl-, *i*-butyl-, (*RS*)-*s*-butyl-, and cyclopentylmagnesium halides led to mixtures of the major *E*-isomers **3c**,**e**–**g** and the minor *Z*-isomers **3′c**,**e**–**g**. Compound **3c** was isolated and characterized as a 98:2 mixture of **3c** and **3′c**, respectively, while isomeric mixtures **3**/**3′e**–**g** were separated by medium pressure liquid chromatography (MPLC) to afford isomerically pure major *E*-isomers **3e**–**g** in 59–78% yields and the minor *Z*-isomers **3′e**–**g** in 2–11% yields. In contrast to reactions with Grignard reagents, transformations of **2** with KCN and 2-methylindole were carried out under acidic conditions to give (1*R*,5*S*)-4-[(*E*)-cyanomethylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**4**) and (1*R*,5*S*)-4-[(*E*)-(2-methyl-1*H*-indol-3-yl)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**5**) in 49% and 31% yield, respectively (Scheme 2).

Structures of compounds **3**–**5** were determined by spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, MS, and HRMS) methods and by elemental analyses. Compounds **3a**,**c**,**e**–**i**, **3′g**, and **5** were not isolated in analytically pure form.



Scheme 2 (i) RMgX, THF, –78 °C to r.t., chromatography; (ii) KCN, HOAc, r.t.; (iii) 2-methyl-1*H*-indole, MeOH, H_2SO_4 (1 equiv), reflux.

Their identities were confirmed by ^{13}C NMR and EI-HRMS. Minor isomer **3′c** was not isolated and was characterized only by ^1H NMR. Due to very small amounts of the isolated minor isomers **3′e**,**f**, compound **3′e** was characterized by ^1H NMR and IR, while **3′f** was characterized by ^1H NMR, IR, EI-MS, and EI-HRMS.

The configuration around the exocyclic C=C double bond in compounds **3a**–**l** were established by NOESY spectroscopy. In the minor isomers **3′e**–**g**, NOE between HC4′ and HC5 was in agreement with the *Z*-configuration, while no NOE between HC4′ and HC5 was observed in the major *E*-isomers **3a**–**l**. (Figure 1).

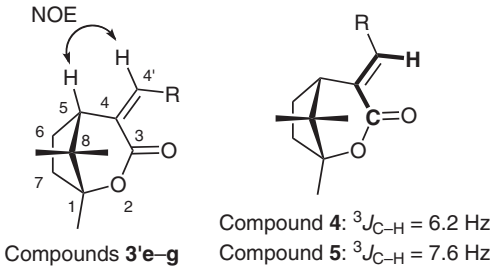


Figure 1 Structure determination by NOESY and HMBC spectroscopy.

In the case of compounds **4** and **5**, the configuration around the exocyclic C=C double bond was studied by HMBC spectroscopy on the basis of long-range coupling constants ($^3J_{C-H}$) between the methylidene proton (HC4′) and the carbonyl carbon atom (O=C3), measured from the antiphase splitting of cross peaks in the HMBC spectrum. Generally, the magnitude of coupling constant, $^3J_{C-H}$, for nuclei with *cis*-configuration around the C=C double bond is smaller (2–6 Hz) than that for *trans*-oriented nuclei (8–12 Hz).[2,7–10] In compound **4**, the magnitude of coupling constant ($^3J_{C-H}$ = 6.2 Hz) showed the *E*-configuration around the exocyclic C=C double bond. However, in compound **5** the magnitude of coupling constant, $^3J_{C-H}$ = 7.6 Hz, could not be used as a reliable criterion for unambiguous determination of configuration around the C=C double bond (Figure 1).

Structures of compounds **3a**, **3l**, **4**, and **5** were determined by X-ray diffraction (Figures 2– 5).

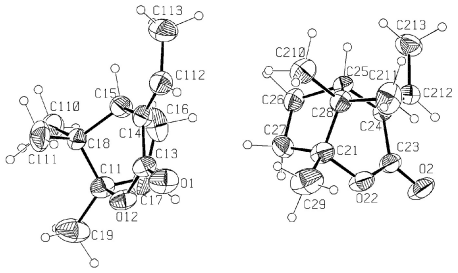


Figure 2 ORTEP view of compound **3a**.

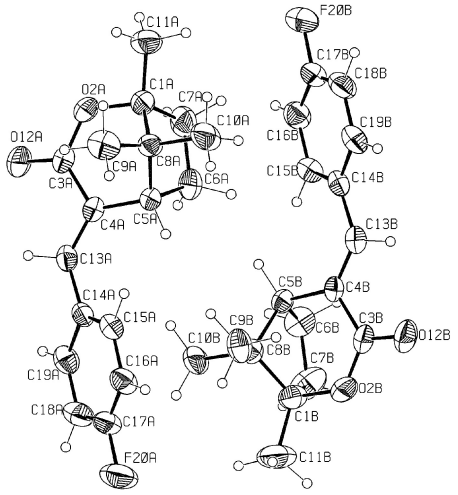


Figure 3 ORTEP view of compound **3l**.

The configurations around the exocyclic C=C double bond in compounds **3a**–**g** and **3′c**,**e**–**g**, derived from alkylmagnesium halides, were correlated with chemical shifts δ for HC4′ and HC5. In the case of the *E*-isomers **3a**–**g**, signals for HC5 appeared at lower field (2.77–2.79 ppm) than in the case of the *Z*-isomers **3′c,e**–**g** (2.35–2.41 ppm). Signals for HC4′ exhibited an even stronger dependence of chemical shift on the configuration, since typical chemical shifts for the HC4′ protons of the *E*-isomers **3a**–**g** were 6.62–6.91 ppm and, in the case of the *Z*-isomers **3′c**,**e**–**g**, 5.61–5.88 ppm (Table 1).

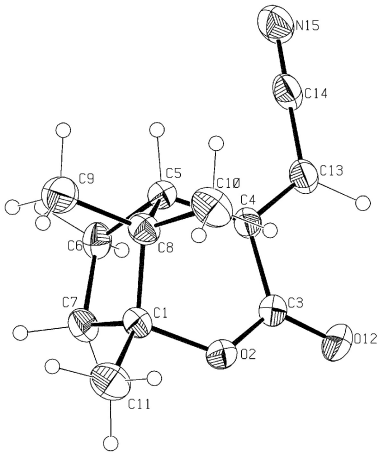


Figure 4 ORTEP view of compound **4**.

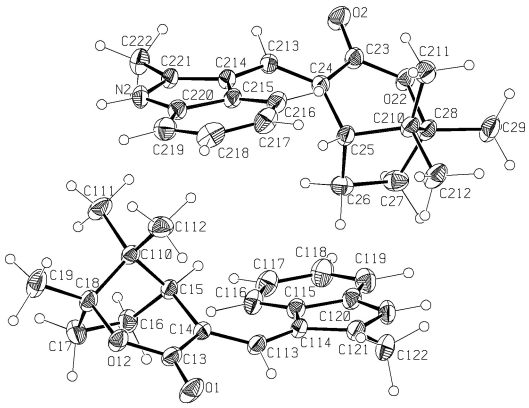


Figure 5 ORTEP view of compound **5**.

In addition to previous reports,[5] especially in connection with the work of Young and co-workers in the field of L-pyroglutamic acid derived enaminones,[5d] the results of this study prove, that coupling of *N*,*N*-dimethyl enamino lactones with Grignard reagents can be successfully employed for introduction of alkylidene residues to active methylene compounds. Besides the most commonly used aldol-type condensations and Wittig-type olefinations, this two step approach represents an alternative methodology for the preparation of various β-substituted α,β-unsaturated acid derivatives.

Melting points were determined on a Kofler micro hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ as solvents and with TMS as the internal standard. Mass spectra were recorded on an AutoSpecQ spectrometer, IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyser 2400. Column chromatography (CC) was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm). Medium pressure liquid chromatography (MPLC) was performed with a Büchi isocratic system with detection on silica gel (Merck, silica gel 60, 0.015–0.035 mm); column dimensions (dry filled): 15 × 460 mm; back pressure: 10–15 bar; detection: UV 254 nm; sample amount: 100–150 mg of isomeric mixture per run. The *Z*/*E* ratios of isomers were determined by ^{1}H NMR.

Table 1 Correlation between the Chemical Shifts (δ) of HC4′ and HC5 Protons and Configuration around the Exocyclic C=C Double Bond in Compounds **3a–g** and **3′c**,**e–g**

Compound	δ (ppm)		*E* or *Z*
	HC4′	HC5	
3a	6.91	2.79	*E*
3b	6.83	2.77	*E*
3c	6.66	2.78	*E*
3d	6.84	2.77	*E*
3e	6.86	2.78	*E*
3f	6.62	2.79	*E*
3g	6.76	2.79	*E*
3′c	5.66	2.35	*Z*
3′e	5.88	2.41	*Z*
3′f	5.61	2.38	*Z*
3′g	5.77	2.37	*Z*

MeMgBr (3M in Et_2O), EtMgBr (1M in THF), *i*-PrMgCl, 2M in Et_2O, *n*-BuMgCl (2M in THF), *i*-BuMgCl (2M in Et_2O), *sec*-BuMgCl (2M in Et_2O), $C_5H_{11}MgCl$ (2M in THF), C_2HMgBr (0.5M in THF), PhMgBr (1M in Et_2O), 4-Me-C_6H_4MgBr (1M in Et_2O), 4-F-C_6H_4MgBr (2M in Et_2O), and 2-methylindole are commercially available (Fluka AG). (1*R*,5*S*)-4-[(*E*)-(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**2**) was prepared according to the procedure described in the literature.[6]

(1*R*,5*S*)-4-Alkylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones 3a–l; General Procedure

A soln of **2** (0.223 g, 1 mmol) in anhyd THF (83 mL) was cooled to –78 °C under argon and a soln of Grignard reagent in THF or Et_2O (6 mmol) was added slowly over a period of 5 min. The mixture was stirred at –78 °C for 1 h, warmed up to r.t. and stirred at r.t. for additional 24 h. Sat. aq NH_4Cl (10 mL) was added, the mixture was stirred at r.t. for 1 h, poured into brine (20 mL), and the product was extracted with CH_2Cl_2 (3 × 70 mL). The organic phases were combined, dried over anhyd Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography (CC, EtOAc–hexanes) followed by medium pressure liquid chromatography (MPLC, EtOAc–hexanes). Fractions containing the product were combined and evaporated in vacuo to give **3**. Experimental, analytical, and spectral data for compounds **3a–l** are given in Tables 2–4.

Table 2 Experimental Data for (1*R*,5*S*)-4-Alkylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **3–5**

Compound	R	*E*:*Z*	Yield (%)	Mp (°C)	Mobile phase (chromatographic method)
3a	Me	100:0	71	80–83 (hexane)	1:4 (CC)[a]
3b	Et	100:0	83	68–74	1:4 (CC)[a]
3c	*i*-Pr	98:2	68	Oil	1:2 (CC),[a] 1:15 (MPLC)[a]
3d	*n*-Bu	100:0	68	Oil	1:5 (CC),[a] 1:6 (MPLC)[a]
3e	*i*-Bu	100:0	59	Oil	1:2 (CC),[a] 1:15 (MPLC)[a]
3′e	*i*-Bu	0:100	2	Oil	
3f	(*RS*)-*s*-Bu	100:0	66	Oil	1:2 (CC)[a], 1:15 (MPLC)[a]
3′f	(*RS*)-*s*-Bu	0:100	7	Oil	
3g	Cyclopentyl	100:0	78	75–78 (heptane)	1:3 (CC),[a] 1:15 (MPLC)[a]
3′g	Cyclopentyl	0:100	11	Oil	
3h	Ethynyl	100:0	35	Oil	1:4 (CC)[a]
3i	$PhCH_2$	100:0	67	Oil	1:2 (CC),[a] 1:6 (MPLC)[a]
3j	Ph	100:0	27	101–102 (hexane)	1:5 (CC)[a]
3k	4-Methylphenyl	100:0	21	93–95 (hexane)	1:5 (CC),[a] 1:10 (MPLC)[a]
3l	4-Fluorophenyl	100:0	64	118–123	100:1 (CC),[b] 1:8 (MPLC)[a]
4	–	100:0	49	147–150	–
5	–	100:0	31	215–222 (CH_2Cl_2–hexane)	–

[a] EtOAc–hexanes.
[b] $CHCl_3$–MeOH.

Table 3 Analytical, MS, and IR Data for (1*R*,5*S*)-4-Alkylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **3–5**

Compound[a]	EI-MS (*m*/*z*) EI-HRMS (*m*/*z*)	IR (cm^{-1})	$[\alpha]_D^{20}$
3a	194 (M^+) Calcd, 194.130680; found, 194.130120	2970, 1713 (CO), 1646, 1381, 1315, 1299, 1268, 1207, 1167, 1142, 1040	+35.2 (*c* 0.128, CH_2Cl_2)
3b[a]	208 (M^+) Calcd, 208.146330; found, 208.146950	2975, 1709 (CO), 1643, 1460, 1384, 1299, 1261, 1207, 1169, 1146, 1050	+56.3 (*c* 0.318, CH_2Cl_2)
3c	222 (M^+) Calcd, 222.161980; found, 222.162350	2963, 1717 (CO), 1645, 1466, 1298, 1260, 1204, 1158, 1143, 1053, 964	+45.6 (*c* 0.272, CH_2Cl_2)
3d[a]	236 (M^+) Calcd, 236.177630; found, 236.177807	2960, 1715 (CO), 1654, 1466, 1394, 1379, 1298, 1269, 1202, 1165, 1144, 1056, 1031	+50.3 (*c* 0.286, $CHCl_3$)
3e	236 (M^+) Calcd, 236.177630; found, 236.178520	2958, 1718 (CO), 1646, 1466, 1379, 1300, 1283, 1202, 1165, 1144, 1034	+53.1 (*c* 0.162, CH_2Cl_2)
3′e		2957, 1717 (CO), 1641, 1466, 1379, 1248, 1221, 1203, 1162, 1137, 1064	

Table 3 Analytical, MS, and IR Data for (1*R*,5*S*)-4-Alkylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **3**–**5** (continued)

Compound[a]	EI-MS (*m*/*z*) EI-HRMS (*m*/*z*)	IR (cm^{-1})	$[\alpha]_D^{20}$
3f	236 (M^+) Calcd, 236.177630; found, 236.178360	2962, 1719 (CO), 1646, 1460, 1377, 1298, 1269, 1203, 1161, 1143, 1055	+45.6 (*c* 0.182, CH_2Cl_2)
3′f	236 (M^+) Calcd, 236.177630; found, 236.177220	2962, 1717 (CO), 1641, 1462, 1377, 1317, 1246, 1203, 1136, 1063, 1018	
3g	248 (M^+) Calcd, 248.177630; found, 248.178350	2957, 2861, 1710 (CO), 1641, 1464, 1448, 1393, 1372, 1315, 1299, 1258, 1207, 1173, 1145, 1106, 1052, 951	+49.3 (*c* 0.134, $CHCl_3$)
3′g	248 (M^+) Calcd, 248.177630; found, 248.176690	2954, 2868, 1719 (CO), 1638, 1466, 1450, 1393, 1380, 1248, 1203, 1161, 1137, 1063, 955	+29.4 (*c* 0.034, $CHCl_3$)
3h	204 (M^+) Calcd, 204.115030; found, 204.115650	2974, 2099 (C≡C), 1710 (CO), 1612, 1467, 1395, 1379, 1301, 1267, 1248, 1202, 1167, 1146, 1068, 1013	+79.6 (*c* 0.093, CH_2Cl_2)
3i	270 (M^+) Calcd, 270.161980; found, 270.162055	2943, 1713 (CO), 1641, 1495, 1468, 1453, 1395, 1380, 1300, 1267, 1202, 1168, 1144, 1035	+50.0 (*c* 0.212, $CHCl_3$)
3j[a]		2970, 1703 (CO), 1622, 1445, 1379, 1296, 1271, 1202, 1142, 1058, 936	+358.0 (*c* 0.188, CH_2Cl_2)
3k[a]		2967, 1708 (CO), 1627, 1513, 1379, 1300, 1270, 1206, 1167, 1143, 1060	+395.8 (*c* 0.118, $CHCl_3$)
3l[a]	274 (M^+) Calcd, 274.136908; found, 274.137550	2974, 1700 (CO), 1628, 1599, 1506, 1384, 1274, 1224, 1207, 1143, 1059	+328.9 (*c* 0.228, $CHCl_3$)
4[a]	205 (M^+) Calcd, 205.110279; found, 205.110850	2969, 2223 (CN), 1716 (CO), 1397, 1321, 1300, 1267, 1175, 1149, 1063	+47.2 (*c* 0.284, CH_2Cl_2)
5[a]	309 (M^+) Calcd, 309.172879; found, 309.173860	3243, 2981, 1677 (CO), 1594, 1459, 1319, 1270, 1240, 1146, 1063	+193.8 (*c* 0.258, CH_2Cl_2)

[a] CHN analysis: C ± 0.4%; H ± 0.4%; N ± 0.2%.

Table 4 NMR Data for (1*R*,5*S*)-4-Alkylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **3**–**5**

Compound	^{1}H NMR (δ)	^{13}C NMR (δ)
3a	0.95, 1.02, 1.32 (9 H, 3 s, 3 × CH_3), 1.44–1.53 (1 H, m, CH*H*), 1.79 (3 H, d, *J* = 7.2 Hz, CH_3C4′), 1.98–2.20 (3 H, m, 3 H, CH_2, C*H*H), 2.79 (1 H, d, *J* = 6.0 Hz, HC5), 6.91 (1 H, dq, *J* = 0.7, 7.2 Hz, HC4′)	13.6, 18.4, 18.9, 23.9, 28.1, 37.3, 44.6, 46.5, 92.5, 134.7, 136.8, 167.5
3b	0.95, 1.01 (6 H, 2 s, 2 × CH_3), 1.05 (3 H, t, *J* = 7.5 Hz, C*H*$_3$CH$_2$), 1.32 (3 H, s, CH_3), 1.44–1.54 (1 H, m, C*H*H), 1.97–2.25 (5 H, m, CH_2, CH*H*, C*H*$_2$CH$_3$), 2.77 (1 H, d, *J* = 6.0 Hz, HC5), 6.83 (1 H, t, *J* = 7.9 Hz, HC4′)	13.6, 18.5, 18.9, 21.3, 23.9, 28.4, 37.3, 44.5, 46.8, 92.6, 133.2, 143.6, 167.6
3c	0.95, 1.02 (6 H, 2 s, 2 × CH_3), 1.028, 1.031 [6 H, 2 d, *J* = 6.7 Hz, (C*H*$_3$)$_2$CH], 1.31 (3 H, s, CH_3), 1.45–1.58 (1 H, m, C*H*H), 1.98–2.22 (3 H, m, C*H*$_2$, CH*H*), 2.54–2.71 [1 H, m, C*H*(CH$_3$)$_2$], 2.78 (1 H, d, *J* = 6.0 Hz, HC5), 6.66 (1 H, d, *J* = 10.2 Hz, H–C4′)	18.1, 18.4, 22.0, 22.3, 23.5, 26.9, 28.1, 36.9, 44.1, 46.6, 92.2, 131.2, 148.2, 167.4
3′c	2.35 (1 H, d, *J* = 6.0 Hz, HC5), 5.66 (1 H, d, *J* = 9.4 Hz, HC4′)	

Table 4 NMR Data for (1*R*,5*S*)-4-Alkylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **3**–**5** (continued)

Compound	^{1}H NMR (δ)	^{13}C NMR (δ)
3d	0.91 [3 H, t, *J* = 7.2 Hz, $H_3C(CH_2)_3$], 0.94, 1.02, 1.32 (9 H, 3 s, 3 × CH_3), 1.28–1.53 (5 H, m, 2 × CH_2, C*H*H), 1.97–2.23 (5 H, m, 2 × CH_2, C*H*H), 2.77 (1 H, d, *J* = 6.0 Hz, HC5), 6.84 (1 H, t, *J* = 7.5 Hz, HC4′)	13.8, 18.1, 18.4, 22.3, 23.5, 27.2, 27.9, 30.7, 36.9, 44.1, 46.4, 92.1, 133.2, 142.0, 167.2
3e	0.93, 0.94 [6 H, 2d, *J* = 6.7 Hz, $(CH_3)_2CH$], 0.95, 1.01, 1.32 (9 H, 3 s, 3 × CH_3), 1.44–1.53 (1 H, m, C*H*H), 1.70–1.85 [1 H, m, C*H*$(CH_3)_2$], 1.97–2.21 (5 H, m, 2 × CH_2, CH*H*), 2.78 (1 H, d, *J* = 6.0 Hz, HC5), 6.86 (1 H, t, *J* = 7.5 Hz, HC4′)	18.1, 18.4, 22.4, 22.6, 23.5, 27.7, 28.2, 36.6, 36.8, 44.2, 46.4, 92.2, 133.7, 140.9, 167.1
3′e	0.91, 0.93 [6 H, 2 d, *J* = 6.8 Hz, $(CH_3)_2CH$], 0.95, 0.98, 1.29 (9 H, 3 s, 3 × CH_3), 1.50–1.63 (1 H, m, C*H*H), 1.65–1.76 [1 H, m, C*H*$(CH_3)_2$], 1.92–2.20 (3 H, m, of CH_2, CH*H*), 2.41 (1 H, d, *J* = 6.4 Hz, HC5), 2.47–5.57 (1 H, m, C*H*H), 2.63–2.73 (1 H, m, CH*H*), 5.88 (1 H, t, *J* = 7.2 Hz, H–C4′)	
3f	0.82–0.88 (3 H, m), 0.94–0.96 (3 H, m), 0.99–1.02 (6 H, m), 1.26–1.55 (3 H, m), 1.32 (3 H, s, CH_3), 1.98–2.23 (3 H, m), 2.30–2.48 (1 H, m), 2.79 (1 H, m), 6.62 (1 H, d, *J* = 10.6 Hz, H–C4′)	11.90, 12.04, 18.00, 18.10, 18.31, 18.34, 19.81, 20.03, 23.41, 23.44, 27.82, 28.17, 29.30, 29.56, 33.87, 33.95, 36.84, 44.08, 44.10, 46.52, 46.62, 92.10, 92.20, 132.02, 132.14, 147.31, 147.32, 167.28, 167.33
3′f	0.81–0.89 (3 H, m), 0.94–0.99 (9 H, m), 1.15–1.45 (2 H, m), 1.29 (3 H, s, CH_3), 1.49–1.61 (1 H, m), 1.92–2.21 (3 H, m), 2.38 (1 H, d, *J* = 6.0 Hz, HC5), 3.47–3.64 (1 H, m), 5.61 (1 H, t, *J* = 10.2 Hz, HC4′)	11.71, 11.92, 18.14, 18.21, 18.22, 18.41, 20.04, 20.08, 23.43, 23.47, 28.24, 28.82, 30.02, 30.26, 33.65, 33.96, 37.03, 44.03, 44.08, 54.64, 54.73, 92.44, 92.59, 131.18, 131.22, 151.42, 151.77, 165.75, 165.82
3g	0.95, 1.01, 1.31 (9 H, 3 s, 3 × CH_3), 1.32–1.43 (2 H, m), 1.45–1.55 (1 H, m), 1.57–1.65 (2 H, m), 1.66–1.88 (4 H, m), 1.97–2.21 (3 H, m), 2.63–2.77 (1 H, m), 2.79 (1 H, d, *J* = 5.7 Hz, HC5), 6.76 (1 H, d, *J* = 10.2 Hz, HC4′)	18.1, 18.4, 23.5, 25.4, 25.5, 28.2, 33.1, 33.3, 36.9, 38.3, 44.1, 46.7, 92.1, 131.8, 146.8, 167.4
3′g	0.95, 0.98 (6 H, 2 s, 2 × CH_3), 1.14–1.23 (2 H, m), 1.29 (3 H, s, CH_3), 1.49–1.70 (5 H, m), 1.84–2.19 (5 H, m), 2.37 (1 H, d, *J* = 6.0 Hz, HC5), 3.74–3.88 (1 H, m), 5.77 (1 H, d, *J* = 9.4 Hz, HC4′)	18.2, 18.3, 23.5, 25.5, 25.6, 28.5, 33.4, 33.7, 37.0, 38.9, 44.1, 54.5, 92.5, 130.6, 150.9, 165.9
3h	0.97, 1.04, 1.34 (9 H, 3 s, 3 × CH_3), 1.51–1.60, 2.01–2.29 (4 H, 2 m, 2 × CH_2), 3.15 (1 H, d, *J* = 6.0 Hz, HC5), 3.51 (1 H, d, *J* = 2.6 Hz, HC≡C), 6.61 (1 H, d, *J* = 2.6 Hz, H–C4′)	18.4, 18.7, 23.7, 27.6, 37.0, 45.2, 49.5, 79.7, 89.7, 94.1, 117.3, 146.4, 166.1
3i	0.98, 1.04, 1.33 (9 H, 3 s, 3 × CH_3), 1.48–1.56, 2.00–2.24 (4 H, 2 m, 2 × CH_2), 2.92 (1 H, d, *J* = 5.7 Hz, HC5), 3.43–3.59 (2 H, m, CH_2Ph), 7.00 (1 H, dt, *J* = 0.8, 7.9, HC4′), 7.15–7.32 (5 H, m, Ph)	18.1, 18.4, 23.4, 27.7, 33.6, 36.8, 44.3, 46.5, 92.3, 126.4, 128.4, 128.6, 133.8, 138.4, 139.2, 166.8
3j	0.99, 1.00, 1.35 (9 H, 3 s, 3 × CH_3), 1.73–1.82, 2.06–2.37 (4 H, 2 m, 2 × CH_2), 3.11 (1 H, d, *J* = 6.4 Hz, HC5), 7.32–7.44 (5 H, m, Ph), 7.76 (1 H, s, HC4′)	18.4, 18.9, 23.9, 28.4, 37.2, 45.0, 47.4, 93.5, 129.0, 129.1, 130.0, 134.1, 135.4, 138.7, 168.2
3k	0.96, 0.99, 1.35 (9 H, 3 s, 3 × CH_3), 1.73–1.82, 2.04–2.35 (4 H, 2 m, 2 × CH_2), 2.38 (3 H, s, CH_3), 3.11 (1 H, d, *J* = 6.4 Hz, HC5), 7.19–7.27 (4 H, m, Ar), 7.73 (1 H, s, HC4′)	17.9, 18.4, 21.3, 23.4, 27.9, 36.8, 44.5, 46.9, 92.8, 129.2, 129.6, 132.1, 132.8, 138.2, 138.9, 167.8
3l	0.96, 1.00, 1.35 (9 H, 3 s, 3 × CH_3), 1.71–1.79, 2.04–2.37 (4 H, 2 m, 2 × CH_2), 3.05 (1 H, d, *J* = 6.0 Hz, HC5), 7.06–7.13 (2 H, m, Ar), 7.30–7.36 (2 H, m, Ar), 7.70 (1 H, s, H–C4′)	18.4, 18.9, 23.9, 28.2, 37.2, 45.0, 47.3, 93.1, 116.1 ($J_{F–C(7')}$ = 21.7 Hz), 131.5 ($J_{F–C(5')}$ = 3.2 Hz), 131.8 ($J_{F–C(6')}$ = 8.2 Hz), 134.0, 137.1, 163.1 ($J_{F–C(8')}$ = 249.9 Hz), 167.5
4	0.99, 1.08, 1.38 (9 H, 3 s, 3 × CH_3), 1.55–1.64, 2.08–2.41 (4 H, 2 m, 2 × CH_2), 3.19 (1 H, d, *J* = 6.8 Hz, HC5), 6.34 (1 H, s, HC4′)	18.4, 18.6, 23.6, 27.2, 36.7, 46.0, 50.9, 95.5, 105.6, 115.5, 154.6, 163.5
5	0.95, 0.99, 1.34 (9 H, 3 s, 3 × CH_3), 1.81–1.90, 2.01–2.12, and 2.21–2.38 (4 H, 3 m, 2 × CH_2), 2.41 (3 H, s, Me), 3.07 (1 H, d, *J* = 6.4 Hz, HC5), 7.09–7.18 (2 H, m, Ar), 7.31–7.34 (1 H, m, Ar), 7.49–7.52 (1 H, m, Ar), 7.81 (1 H, s, HC4′), 8.70 (1 H, br s, NH)	13.2, 18.5, 18.8, 24.0, 28.8, 37.3, 44.9, 48.4, 93.6, 109.3, 111.3, 120.0, 120.6, 122.1, 127.4, 131.6, 132.8, 136.0, 137.1, 168.9

(1*R*,5*S*)-4-[*(E)*-Cyanomethylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (4)

KCN (0.130 g, 2 mmol) was added to a soln of **2** (0.223 g, 1 mmol) in HOAc (100%, 3 mL) and the mixture was stirred at r.t. for 5 d. Volatile components were evaporated in vacuo and CH_2Cl_2 (20 mL) was added to the residue. The so formed suspension was filtered, the undissolved material was washed with CH_2Cl_2 (50 mL), and the filtrate was evaporated in vacuo. The residue was purified by CC (EtOAc–hexanes, 1:10). Fractions containing the product were combined and evaporated in vacuo to give **4**. Experimental, analytical, and spectral data for compound **4** are given in Tables 2–4.

(1*R*,5*S*)-4-[*(E)*-(2-Methyl-1*H*-indol-3-yl)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (5).

A soln of H_2SO_4 acid in anhyd MeOH (1 M, 0.5 mL, 0.5 mmol) was added to the soln of **2** (0.223 g, 1 mmol) and 2-methyl-1*H*-indole (0.131 g, 1 mmol) in anhyd MeOH (3 mL) and the mixture was heated under reflux for 5 h. Volatile components were evaporated in vacuo and the residue was purified by CC (EtOAc–hexanes, 1:2). Fractions containing the product were combined and evaporated in vacuo to give **5**. Experimental, analytical, and spectral data for compound **5** are given in Tables 2–4.

X-Ray Structure Analysis

Single crystal X-ray diffraction data of compounds **3a**, **3l**, **4**, and **5** were collected at r.t. on a Nonius Kappa CCD diffractometer (Mo-Kα radiation) using the Nonius Collect Software.[11] DENZO and SCALEPACK[12] were used for indexing and scaling of the data. The structures were solved by means of SIR97.[13] Refinement was done using Xtal3.4[14] program package and the crystallographic plots were prepared by ORTEP III.[15] Crystal structures were refined on *F* values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically in all cases. The positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina[16] weighting scheme was used in all cases.

Crystal data are given in Table 5. Bond lengths and angles are omitted as they are all within expected ranges and the details can be found in the deposited material.[17]

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Crystallographic data were collected on the Kappa CCD Nonius diffractometer in the Laboratory of Inorganic Chemistry, Faculty of Chemistry and chemical Technology, University of Ljubljana, Slovenia. We acknowledge with thanks the financial contribution of the Ministry of Science and technology, Republic of Slovenia through grant Packet X-2000 and PS-511-102, which thus made the purchase of the apparatus possible.

References

(1) (a) Money, T. *Nat. Prod. Rep.* **1985**, 253. (b) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. (c) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241. (d) Money, T. *Remote Functionalization of Camphor: Application to Natural Product Synthesis in Organic Synthesis: Theory and Applications*, Vol 3; JAI Press Inc.: Greenwich, London, **1996**, 1.

(2) For recent reviews see: (a) Stanovnik, B.; Svete, J. *Synlett* **2000**, 1077. (b) Stanovnik, B.; Svete, J. In *Targets in Heterocyclic Systems*, Vol. 4; Italian Society of Chemistry: Roma, **2000**, 105. (c) Svete, J. *J. Heterocycl. Chem.* **2002**, *39*, 437. (d) Svete, J. *Monatsh. Chem.* **2004**, *135*, 629. (e) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433.

Table 5 Crystal Data for Compounds **3a**, **3l**, **4**, and **5**[17]

Copound	**3a**	**3l**	**4**	**5**
Formula	$C_{12}H_{18}O_2$	$C_{17}H_{19}FO_2$	$C_{12}H_{15}NO_2$	$C_{20}H_{23}NO_2$
System	monoclinic	monoclinic	orthorhombic	monoclinic
Sp. group	$P2_1$	$P2_1$	$C222_1$	$P2_1$
a (Å)	8.0442(2)	10.9342(2)	7.54390(10)	11.2229(2)
b (Å)	13.2697(3)	11.9219(2)	11.5398(2)	11.5846(2)
c (Å)	10.6110(3)	11.9019(2)	25.5523(5)	13.3444(3)
β (°)	93.6516(10)	107.7885(10)	90	104.8836(9)
Vol. (Å^3)	1130.36(5)	1477.31(5)	2224.46(7)	1676.74(6)
Z[a]	2	2	8	2
Z′[b]	4	4	8	4
R_w[c]	0.041	0.032	0.039	0.040

[a] Z: Multiplicity of the space group.
[b] Z′: Number of molecules in the unit cell.
[c] R_w given for 'observed' reflections ($I > 2\sigma(I)$).

(3) (a) Pirc, S.; Bevk, D.; Golič Grdadolnik, S.; Svete, J. *ARKIVOC* **2003**, *Part xiv*, 37. (b) Westman, J.; Lundin, R. *Synthesis* **2003**, 1025. (c) Čebašek, P.; Wagger, J.; Bevk, D.; Jakše, R.; Svete, J.; Stanovnik, B. *J. Comb. Chem.* **2004**, *6*, 356.
(4) Benary, E. *Chem. Ber.* **1931**, *64*, 2543.
(5) (a) Ziegler, F. E.; Guenther, T.; Nelson, R. V. *Synth. Commun.* **1980**, *10*, 661. (b) Asokan, C. V.; Balu, M. P.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 727. (c) Hutchinson, J. H.; Money, T. *Tetrahedron Lett.* **1985**, *26*, 1819. (d) Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3519.
(6) (a) Abdulla, R. F.; Fuhr, K. H. *J. Org. Chem.* **1978**, *43*, 4248. (b) Sanin, A. V.; Nenajdenko, V. G.; Smolko, K. I.; Denisenko, D. I.; Balenkova, E. S. *Synthesis* **1998**, 842.
(7) Grošelj, U.; Rečnik, S.; Svete, J.; Meden, A.; Stanovnik, B. *Tetrahedron: Asymmetry* **2002**, *13*, 821.
(8) Grošelj, U.; Bevk, D.; Jakše, R.; Meden, T.; Pirc, S.; Rečnik, S.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2004**, *15*, 2367.
(9) (a) Titman, J. J.; Foote, J.; Jarvis, J.; Keeler, J.; Neuhaus, D. *J. Chem. Soc., Chem. Commun.* **1991**, 419. (b) Ando, T.; Koseki, N.; Toia, R. F.; Casida, J. E. *Magn. Res. Chem.* **1993**, *31*, 90. (c) Fischer, P.; Schweizer, E.; Langner, J.; Schmidt, U. *Magn. Res. Chem.* **1994**, *32*, 567.
(10) (a) Golič-Grdadolnik, S.; Stanovnik, B. *Magn. Res. Chem.* **1997**, *35*, 482. (b) Škof, M.; Svete, J.; Stanovnik, B.; Golič, L.; Golič-Grdadolnik, S.; Selič, L. *Helv. Chim. Acta* **1998**, *81*, 2332. (c) Baš, J.; Rečnik, S.; Svete, J.; Golič-Grdadolnik, S.; Stanovnik, B. *ARKIVOC* **2001**, *Part ii*, 61. (d) Bevk, D.; Kmetič, M.; Rečnik, S.; Svete, J.; Golič, L.; Golobič, A.; Stanovnik, B. *Chem. Heterocycl. Compd.* **2001**, 1651. (e) Jakše, R.; Rečnik, S.; Svete, J.; Golobič, A.; Golič, L.; Stanovnik, B. *Tetrahedron* **2001**, *57*, 8395. (f) Jakše, R.; Krošelj, V.; Rečnik, S.; Soršak, G.; Svete, J.; Stanovnik, B.; Golič-Grdadolnik, S. *Z. Naturforsch., B: Chem. Sci.* **2002**, *57*, 453. (g) Pirc, S.; Rečnik, S.; Škof, M.; Svete, J.; Golič, L.; Meden, A.; Stanovnik, B. *J. Heterocycl. Chem.* **2002**, *39*, 411.
(11) *Collect Software*; Nonius BV: Delft, The Netherlands, **1998**.
(12) Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307.
(13) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **1999**, *32*, 115.
(14) Hall, S. R.; King, G. S. D.; Stewart, J. M. *The Xtal 3.4 User's Manual*; University of Western Australia: Lamb, Perth, **1995**.
(15) Burnett, M. N.; Johnson, C. K. *ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations*; Oak Ridge National Laboratory Report: USA, **1996**, ORNL-6895.
(16) Wang, H.; Robertson, B. E. *Structure and Statistics in Crystallography*; Wilson, A. J. C., Ed.; Adenine Press: New York, **1985**.
(17) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 254265-254268. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.