# A Convenient Transformation of 2-Alkylidenecycloalkanones into Alkyl-Substituted Bicyclo[*n*.1.0]alkan-1-ols: Application to the Synthesis of Capsaicin

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Dedicated to Dr. Jean Ollivier on the occasion of his 60th birthday

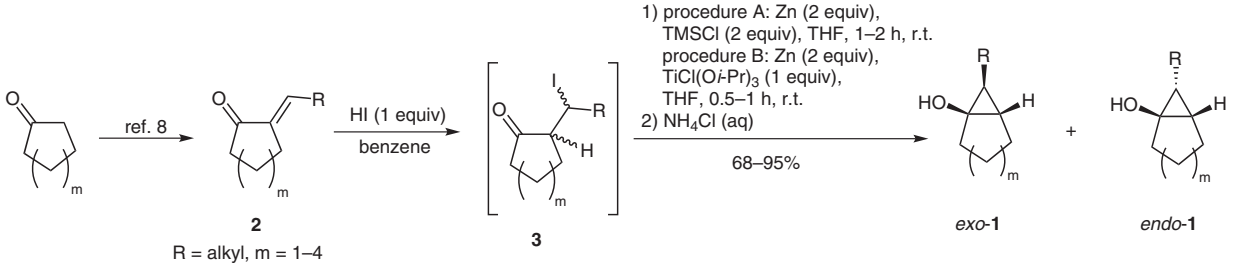
**Abstract:** Treatment of 2-alkylidenecycloalkanones with hydrogen iodide in benzene and subsequent reaction of the obtained β-iodo ketones with zinc dust in THF in the presence of chlorotrimethylsilane or titanium(IV) chlorotriisopropoxide led to *exo*- and *endo*-(*n*+3)-alkylbicyclo[*n*.1.0]alkan-1-ols in high yields. Cyclization of the intermediate β-iodo ketones under these conditions proceeded in a moderate to good diastereoselectivity, and the resulted bicyclic cyclopropanols were easily separated by column chromatography over silica gel. *exo*-7-Isopropylbicyclo[4.1.0]heptan-1-ol obtained in this manner was efficiently employed as a key intermediate in the synthesis of capsaicin.

**Key words:** cyclopropanols, stereoselectivity, ring closure, ring opening, capsaicin

Substituted cyclopropanols and their derivatives are useful synthetic intermediates and could be prepared by various methods, including cyclopropanation of carboxylic esters with alkoxytitanacyclopropane reagents, cycloaddition of carbenoid reagents to unsaturated compounds as well as reactions of 1,3-cyclization.[1] In the latter case, the precursors of the cyclopropanols are β-halogenocarbonyl compounds.[2] Thus, Narasimhan and Patil reported the transformation of β-iodo ketones into the corresponding cyclopropanols under the treatment with an excess of zinc dust (20 equiv) and trimethylchlorosilane (6 equiv) in refluxed THF.[3–5] During our studies on the stereochemistry of cyclization of acyclic β-metallo ketones, we have recently found that the transformation of β-iodo ketones into 1,2-disubstituted cyclopropanols proceeded smoothly at room temperature under the treatment with close to equimolecular amounts of the same combination of the reagents.[6] It was attractive to extend this convenient procedure for the preparation of cyclopropanols to the synthesis of bicyclic analogues **1**, bearing alkyl substituents in cyclopropane ring. Although such kind of compounds has a considerable synthetic potential,[1c] to our knowledge, their preparation was limited by the synthesis of TMS-protected bicyclo[*n*.1.0]alkan-1-ols, bearing methyl substituent at the three-carbon ring, by the reaction of cyclic silyl enol ethers with the carbenoid reagent, generated from zinc and 1,1-diiodoethane.[7]

In this work, it was found that easily available 2-alkylidenecycloalkanones **2**[8] are more suitable intermediates for the preparation of (*n*+3)-alkylbicyclo[*n*.1.0]alkan-1-ols **1** by means of 1,3-elimination reactions. Unsaturated ketones **2**, obtained by the condensation of the corresponding cycloalkanones with aldehydes[8a–e] were transformed into the corresponding β-iodo ketones **3** by treatment with gaseous hydrogen iodide or iodotrimethylsilane in aprotic solvents and followed by aqueous work-up of the reaction mixtures (Scheme 1).[9,10] In comparison with acyclic β-iodo ketones,[6] compounds **3** were considerably less stable and all our attempts to isolate them in pure form were unsuccessful.[11] Addition of the prepared solutions of β-iodo ketones **3** to the mixture of zinc dust (2 equiv) and trimethylchlorosilane (2 equiv) in THF led to the formation of the corresponding bicyclic cyclopropanols **1**, however, the yields of the products **1** were hardly reproducible and did not exceed 60%.

We have found with pleasure, that compounds **1** could be smoothly obtained in reproducible yields if β-iodo ketones **3** were prepared immediately before the cyclization by the addition of an equimolecular amount of hydrogen iodide to the solutions of unsaturated ketones **2** in dry ben-




**Scheme 1**

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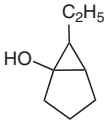
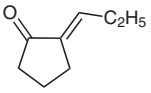
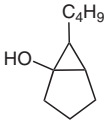
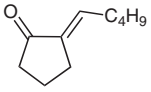
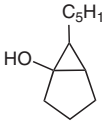
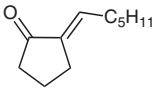
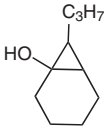
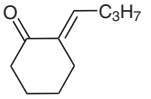
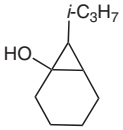
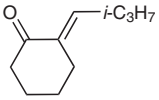
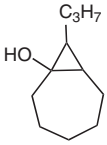
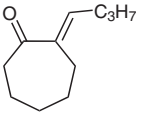
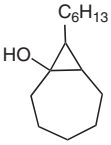
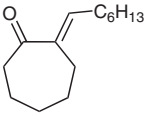
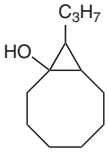
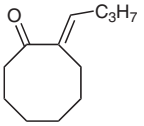
**Table 1** Preparation of (*n*+3)-Alkylbicyclo[*n*.1.0]alkan-1-ols **1**

| Entry | Bicyclo[*n*.1.0]-alkan-1-ol **1** | Starting ketone **2** | Procedure[a] | Yield (%)[b] *exo*-**1** | Yield (%)[b] *endo*-**1** |
|---|---|---|---|---|---|
| 1 |  **1a** |  **2a** | A<br>B | 60<br>65 | 24<br>9 |
| 2 |  **1b** |  **2b** | A<br>B | 59<br>57 | 22<br>25 |
| 3 |  **1c** |  **2c** | A | 58 | 22 |
| 4 |  **1d** |  **2d** | A | 63 | 20 |
| 5 |  **1e** |  **2e** | A<br>B | 68<br>87 | 5[c]<br>8 |
| 6 |  **1f** |  **2f** | A | 62 | 12 |
| 7 |  **1g** |  **2g** | A | 68 | 15 |
| 8 |  **1h** |  **2h** | A<br>B | 50<br>67 | 18<br>28 |

[a] Procedure A: 1) HI (1 equiv); 2) Zn (2 equiv), TMSCl (2 equiv), THF, r.t. Procedure B: 1) HI (1 equiv); 2) Zn (2 equiv), $TiCl(O\textit{i}\text{-}Pr)_3$ (1 equiv), THF, r.t.

[b] Isolated yields.

[c] Estimated by $^1$H NMR, product was isolated in impure form.

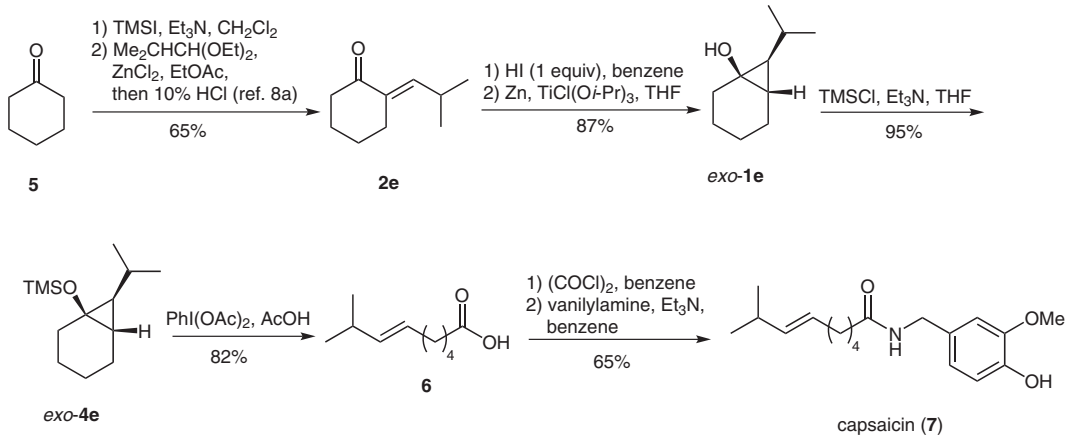
zene (Scheme 1, procedure A).[12,13] Under these conditions, unsaturated ketones **2a**–**h** led to the mixtures of stereoisomeric bicyclic cyclopropanols **1a**–**h** in 68–84% combined yields (Table 1, procedure A). In all cases, *exo*-diastereoisomers **1a**–**h** were isolated as major products. Diastereomeric alcohols *exo*-**1a**–**h** and *endo*-**1a**–**h** were easily separated by column chromatography over silica gel, and *endo*-isomers demonstrated lower $R_f$ values in comparison with corresponding *exo*-isomers.[14,15]

Although 2-alkylidenecycloalkanones **2a**–**d**,**f**–**h** with unbranched substituents afforded corresponding bicyclic cyclopropanols **1a**–**d** and **1f**–**h** with moderate *exo* diastereoselectivity, in the case of ketone **2e** with more bulky isopropyl substituent, the diastereoselectivity was higher (Table 1, entry 5). *exo*-Bicyclic cyclopropanol *exo*-**1e** was obtained in 68%, and no increase in yield was observed after prolonged reaction time (24 h) or when the reaction was carried out in refluxing THF. 2-Isobutylcyclohexanone (ca. 30 mol%) was detected in this case as a major byproduct by $^1$H NMR spectroscopy. Moderate yield of *exo*-**1e** could be attributed to a higher content of the corresponding β-zinc ketone in equilibrium with the sterically hindered zinc cyclopropanolate.[16]

Assuming more steric bulkiness of β-titano ketones in comparison with β-zinc ketones,[6] we attempted to increase yields and stereoselectivity of the cyclization by the use of titanium(IV) chlorotriisopropoxide as a promoting reagent (Scheme 1, procedure B).[4,17] Indeed, the addition of the solution of β-iodo ketone **3e** in benzene to suspension of zinc dust (2 equiv) in THF in the presence of $TiCl(O\textit{i}\text{-}Pr)_3$ (1 equiv) at room temperature led to the reaction, and in the formation of cyclopropanols **1e** in 95% overall yield (*exo*/*endo* = 91:9, Table 1, entry 5, procedure B). For the case of the zinc-induced cyclization of ketone **2h** in the presence of $TiCl(O\textit{i}\text{-}Pr)_3$, the yield of the corresponding cyclopropanols **1h** increased to 95%, in comparison with 68% overall yield, obtained in the presence of TMSCl. However, the ratio of *exo*/*endo* diastereomers remained nearly the same (Table 1, entry 8). In the case of cyclopentane derivative **2b** both procedures gave similar results in respect to diastereoselectivity and yields of the products **1b** (Table 1, entry 2), whereas in the case of compound **2a** yield of *endo*-isomer **1a** decreased under the conditions of procedure B (Table 1, entry 1).

To demonstrate a synthetic utility of bicyclic cyclopropanols **1**, we used compound *exo*-**1e** as a key intermediate in a new synthesis of capsaicin[18] starting from cyclohexanone **5** (Scheme 2). Oxidative fragmentation of the trimethylsilyl ether *exo*-**4e**, prepared from cyclopropanol *exo*-**1e**, by treatment with phenyliodosodiacetate in acetic acid[7c–e,19] afforded *trans*-8-methyl-6-nonenoic acid (**6**) in 82% yield.[20] The acid **6** was transformed into the corresponding acid chloride[18h] and subsequent acylation by the latter of vanilylamine led to capsaicin **7**[21] in 29% overall yield based on cyclohexanone **5**.

In conclusion, we elaborated an efficient procedure for the preparation of (*n*+3)-alkylbicyclo[*n*.1.0]alkan-1-ols **1** from easily available 2-alkylidenecycloalkanones **2** by treatment of the latter with an equimolecular amount of hydrogen iodide in dry benzene and subsequent intramo-




**Scheme 2**

lecular cyclization of β-iodo ketones **3**. The *exo*- and *endo*-diastereomers of bicyclic alcohols **1** are easily separable by column chromatography, and could be employed as useful synthetic intermediates for the stereoselective preparation of pure alkenoic acids by the oxidative ring cleavage as it was illustrated by a convenient synthesis of capsaicin **7** from cyclohexanone **5**.

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(11) Compounds **3** could be stored in solution at r.t. for a few hours without noticeable decomposition.


(12) **General Procedure for the Preparation of (*n*+3)-Alkylbicyclo[*n*.1.0]alkan-1-ols 1 in the Presence of TMSCl as Activating Reagent (Procedure A)**

Chlorotrimethylsilane (6.3 mL, 50 mmol) was added to the suspension of zinc dust (3.25 g, 50 mmol) in THF (25 mL), the resulted mixture was sealed with a rubber septum and stirred for 5–10 min. An equivalent amount of solution of HI in dry benzene (ca. 0.5–1.5 M)[22] was added in 1–2 min to the solution of an unsaturated ketone **2** (25 mmol) in dry benzene (15 mL). Freshly prepared red-brown solutions of β-iodo ketones **3** were added in one portion within 1–2 min via syringe to the suspension of zinc dust. After a few minutes an exothermic reaction started, and the reaction mixture became colorless. When the reaction was completed (1–2 h, TLC monitoring) the mixture was poured into sat. solution of $NH_4Cl$ (50 mL), the organic layer was separated, and the aqueous phase was extracted with $Et_2O$ (3 × 15 mL).

The combined organic phases were washed with sat. solutions of $NaHCO_3$, NaCl, and dried with $Na_2SO_4$. Solvent was removed under reduced pressure, and compounds **1** were isolated as colorless oils or white crystalline solids by column chromatography over silica gel, treated with $Et_3N$ (ca. 0.1 mL per 2 g of $SiO_2$; eluent: PE–EtOAc; see Table 1).

(13) $^1$H NMR spectra of the solutions of β-iodo ketones **3** demonstrated the absence of the olefinic proton signals of starting compounds **2**. The multiplet signals from protons of CHI groups in diastereomeric β-iodo ketones were observed at δ = 4.0–4.5 ppm.

(14) Stereochemical configurations for compounds **1a** were confirmed by 1D NOESY experiments, which were carried out with their trimethylsilyl ethers **4a**. Irradiation of signal of TMS group led to enhancement of signals from both cyclopropane protons at δ = 1.06 and 1.37 ppm in the case of *endo*-isomer, whereas in the same experiment for *exo*-isomer the signal of cyclopropane proton at δ = 0.87 ppm and the signals of ethyl $CH_2$ group (δ = 1.22 and 1.53 ppm) were enhanced. Values of $^3J$ coupling constants between the cyclopropyl protons ($J$ = 4.0 Hz and 7.3 Hz for *exo*- and *endo*-isomers of **1a**, respectively) are also agreed with the stereochemical assignment.

(15) **Analytical Data of Selected Compounds 2**

***exo*-6-Ethylbicyclo[3.1.0]hexan-1-ol (*exo*-1a)**

Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.69 (dt, $J_1$ = 7.2 Hz, $J_2$ = 4.0 Hz, 1 H), 0.87 (t, $J$ = 4.0 Hz, 1 H), 0.99 (t, $J$ = 7.3 Hz, 3 H), 1.12 (m, 1 H), 1.35–1.57 (m, 3 H), 1.60 (br s, 1 H, OH), 1.65 (m, 1 H), 1.85 (m, 1 H), 1.92–1.98 (m, 2 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 14.37, 20.44, 21.79, 26.80, 26.90, 29.54, 34.49, 68.02. IR ($CCl_4$) = 3603, 3400, 3027 cm$^{-1}$. Anal. Calcd for $C_8H_{14}O$ (126.20): C, 76.14; H, 11.18. Found: C, 76.30; H, 11.10.

***endo*-6-Ethylbicyclo[3.1.0]hexan-1-ol (*endo*-1a)**

Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, $J$ = 7.3 Hz, 3 H), 1.13 (m, 1 H), 1.18–1.41 (m, 4 H), 1.46 (ddd, $J_1$ = 12.5 Hz, $J_2$ = 9.7 Hz, $J_3$ = 2.5 Hz, 1 H), 1.86 (m, 1 H), 1.96–2.13 (m, 4 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 14.54, 16.55, 24.22, 24.92, 29.26, 31.97, 32.10, 69.41. IR ($CCl_4$) = 3596, 3338, 3027. Anal. Calcd for $C_8H_{14}O$ (126.20): C, 76.14; H, 11.18. Found: C, 76.33; H, 11.28.

***exo*-7-Isopropylbicyclo[4.1.0]heptan-1-ol (*exo*-1e)**

Colorless crystalls, mp 52.4–53.1 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.22 (dd, $J_1$ = 6.0, $J_2$ = 9.9 Hz, 1 H), 0.70 (ddd, $J_1$ = 1.6 Hz, $J_2$ = 6.0 Hz, $J_3$ = 7.8 Hz, 1 H), 0.96 (d, $J$ = 6.7 Hz, 3 H), 1.01 (d, $J$ = 6.7 Hz, 3 H), 1.08 (m, 1 H), 1.21 (m, 2 H), 1.35 (m, 1 H), 1.45 (m, 2 H), 1.71 (br s, 1 H, OH), 1.86 (ddd, $J_1$ = 5.6 Hz, $J_2$ = 9.9 Hz, $J_3$ = 13.1 Hz, 1 H), 1.97 (m, 1 H), 2.05 (m, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 21.44, 21.79, 22.50, 23.21, 24.47, 24.51, 28.10, 33.04, 37.50, 58.52. IR ($CCl_4$) = 3604, 2995. Anal. Calcd for $C_{10}H_{18}O$ (154.25): C, 77.87; H, 11.76. Found: C, 77.69; H, 11.85.

(16) (a) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056. (b) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079. (c) Casey, C. P.; Strotman, N. A. *Can. J. Chem.* **2006**, *84*, 1208.

(17) **General Procedure for the Preparation of (*n*+3)-Alkylbicyclo[*n*.1.0]alkan-1-ols 1 in the Presence of $TiCl(O$*i*$-Pr)_3$ as Activating Reagent (Procedure B)**

A solution $TiCl(O$*i*$-Pr)_3$ in THF (1 M, 25 mmol, 25 mL) was added to the suspension of zinc dust[23] (3.25 g, 50 mmol) in THF (25 mL). Immediately, a solution of β-iodo ketone **3** (25 mmol) in dry benzene (prepared as described above in procedure A) was added. During few minutes, the reaction mixture spontaneously warmed up and turned dark brown. When the reaction was completed (0.5–1 h, TLC monitoring), sat. solution of $NH_4Cl$ (10 mL) was added to the mixture, precipitate was filtered off and washed thoroughly with $Et_2O$ (5 × 15 mL). The filtrate was washed with sat. solution of NaCl, dried with $Na_2SO_4$. The solvent was removed under reduced pressure, and compounds **1** (see Table 1, entries 1, 2, 5, and 8) were isolated by column chromatography over silica gel, treated with $Et_3N$ (ca. 0.1 mL per 2 g of $SiO_2$; eluent: PE–EtOAc).

(18) (a) Späth, E.; Darling, S. F. *Ber. Dtsch. Chem. Ges. B* **1930**, *63*, 737. (b) Crombie, L.; Dandegaonker, S. H.; Simpson, K. B. *J. Chem. Soc.* **1955**, 1025. (c) Takahashi, M.; Osawa, K.; Ueda, J.; Okada, K. *Yakugaku Zasshi: J. Pharm. Soc. Jpn.* **1976**, *96*, 1000. (d) Vig, O. P.; Aggarwal, R. C.; Sharma, M. L.; Sharma, S. D. *Indian J. Chem., Sect. B.: Org. Chem. Incl. Med. Chem.* **1979**, *17*, 558. (e) Gannett, P. M.; Nagel, D. L.; Reilly, P. J.; Lawson, T.; Sharpe, J.; Toth, B. *J. Org. Chem.* **1988**, *53*, 1064. (f) Kaga, H.; Miura, M.; Orito, K. *J. Org. Chem.* **1989**, *54*, 3477. (g) Kaga, H.; Goto, K.; Fukuda, T.; Orito, K. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 946. (h) Kaga, H.; Goto, K.; Takahashi, T.; Hino, M.; Tokuhashi, T.; Orito, K. *Tetrahedron* **1996**, *52*, 8451.

(19) The fragmentation of trimethylsilyl ether *exo*-**4e** was carried out in AcOH in accordance to the procedure, described by Kirihara et al., see ref. 7e. Cyclopropanol *exo*-**1e** under these conditions afforded acid **6** in 50–60% yield.

(20) Spectral data are consistent with those previously reported for this compound in ref. 18h. On the basis of NMR and GC data, the stereochemical purity of *trans*-configured carbon–carbon double bond in acid **6** was more than 99%.

(21) Spectral data are consistent with those previously reported for this compound in ref. 18h.

(22) (a) Prepared by passing a stream of gaseous HI, generated by dropping 57% HI upon $P_2O_5$.[22b] The concentration of HI in the obtained solution was determined after its aqueous workup by titration with sodium hydroxide. (b) Dillon, R. T.; Young, W. G. *J. Am. Chem. Soc.* **1929**, *51*, 2389.

(23) Zinc dust was previously activated with few drops of DBE or TMSCl.