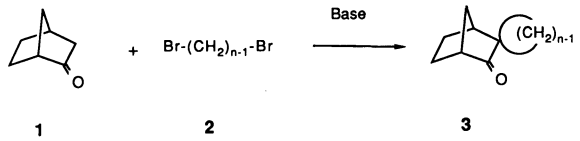
A Convenient Synthesis of Spironorcamphors

Kimihiko HORI, Naotake TAKAISHI,* and Yoshiaki INAMOTO
Tochigi Research Laboratories, Kao Corporation,
2606 Akabane, Ichikaimachi, Tochigi 321-34
(Received November 30, 1987)

Synopsis. The effects of the base, molar ratio of the reagent, solvent and reaction temperature on the cycloalkylation of norcamphor with 1,4-dibromobutane were explored, and optimum conditions for the preparation of spiro[bicyclo[2.2.1]heptane-2,1′-cyclopentan]-3-one have been established. 3-*exo*-(4-Bromobutyl)norcamphor was isolated and characterized as a reaction intermediate. A series of spironorcamphors with various ring sizes were obtained in good yields using a 1:1.5:2.5 ratio of norcamphor/α,ω-dibromoalkanes /$NaNH_2$ in Et_2O.

The syntheses and reactions of spiro compounds have attracted considerable attention in recent years.[1] As one part of our continuing interest in the chemistry of tricycloundecane derivatives,[2] we have required a convenient method for the preparation of spiro[bicyclo[2.2.1]heptane-2,1′-cyclopentan]-3-one (**3c**).[2d] It seemed that the most direct route to **3c** would be cycloalkylation[1b,3] of norcamphor (bicyclo[2.2.1]heptan-2-one **1**) with 1,4-dibromobutane (**2c**) in the presence of the base.

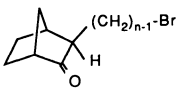


1 **2** **3**

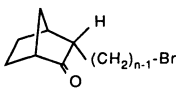
a : n=3
b : n=4
c : n=5
d : n=6
e : n=7

Although a lot of examples for the synthesis of spiroketones via cycloalkylation have been described,[1b] a survey of the literature has indicated that only one example has been reported by Sauers et al.,[4] on the reaction of **1**, giving spiro[bicyclo[2.2.1]heptane-2,1′-cyclobutan]-3-one (**3b**) in low yield by treatment with 1,3-dibromopropane (**2b**) in the presence of $NaNH_2$. We now report on a general method for the synthesis of spironorcamphors (**3**) involving the cycloalkylation of **1** with α,ω-dibromoalkanes (**2**) in the presence of a base.

Initial attempts to alkylate **1** with **2c** to the spiroketone **3c** were carried out under similar conditions employed for the preparation of **3b**.[4] Treatment of **1** with $NaNH_2$ (3 equiv) in Et_2O gave an enolate which upon treatment with **2c** (10 equiv) at ambient temperature for 48 h afforded **3c** (48%) along with monoalkylated product, 3-*exo*-(4-bromobutyl)-norcamphor (*exo*-**4c**, 31%) (Table 1, entry 1). The structure of **3c** was confirmed by a comparison of the physical properties with previously reported data.[2d] The configuration of the substituent of *exo*-**4c** was evidenced by comparing the ^{13}C NMR chemical shifts with those of the related 3-alkylnorcamphors.[5] A marked upfield shift at C-7 was observed due to the presence of an exo substituent at C-3 in *exo*-**4c**, which can be classified as a γ-syn effect.[5]



exo- **4**



endo- **4**

Table 1. Reaction of Norcamphor (**1**) with 1,4-Dibromobutane (**2c**)

Entry	Equiv of **2c**	Base (equiv)	Solvent	Reaction temp	Reaction time/h	Yield/%[a]	
						3c	*exo*-**4c**
1	10	$NaNH_2$ (3.0)	Et_2O	r.t.	48	48	31
2	10	$NaNH_2$ (2.5)	Et_2O	Reflux	24	48	31
3	6	$NaNH_2$ (2.5)	Et_2O	Reflux	24	55	26
4	3	$NaNH_2$ (2.5)	Et_2O	Reflux	24	67	
5	1.5	$NaNH_2$ (2.5)	Et_2O	Reflux	24	67	
6	1.5	$NaNH_2$ (3.0)	Et_2O	Reflux	24	67	
7	1.5	$NaNH_2$ (2.5)	Hexane	Reflux	12	48	
8	1.5	$NaNH_2$ (2.5)	Toluene	Reflux	1	24	
9	1.5	$NaNH_2$ (2.5)	Toluene	40°C	12	41	
10	1.5	*t*-BuOK (2.5)	Benzene	Reflux	3	53	
11	10	*t*-BuOK (2.5)	Benzene	Reflux	3	45	9
12	1.5	LDA (2.5)	THF	−78°C→r.t.	60	8	33
13	1.2	LDA (1.2)	THF	−78°C→r.t.	60	12	41

a) Determined by GLC analysis using dodecane as an internal standard.

The exclusive formation of the *exo*-**4c** is rationalized based on a selective exo attack of the alkylating reagent **2c**.[6] The isolated ketone *exo*-**4c** was cyclized in the presence of $NaNH_2$ to afford **3c** in 89% yield.[7] This means that *exo*-**4c** is the intermediate in the above-mentioned cycloalkylation reaction. The lack of its epimer, *endo*-**4c**, implies a rapid cyclization of the enolate anion derived from *exo*-**4c**, compared to a proton-exchange reaction.[8]

Various efforts were devoted to optimize the yield of **3c**. Similar results were obtained through a treatment of a mixture of **1** and **2c** with $NaNH_2$ in boiling Et_2O[9] (entry 2). However, the yield and selectivity of **3c** were highly increased upon decreasing the amounts of **2c** (entries 3—6). The highest yield of **3c** could be attained when the reaction was performed using a 1:1.5:2.5 ratio of **1**/**2c**/$NaNH_2$ in Et_2O (entry 5). A large excess of **2c** caused side reactions with $NaNH_2$.

The use of hexane (entry 7) or toluene (entries 8 and 9) instead of Et_2O gave a decreased yield of **3c**. It has been reported[10] that cyclohexanone affords spiro[4.5]-decan-6-one in 70% yield when treated with **2c** in the presence of potassium *t*-butoxide (*t*-BuOK). By using these conditions, we obtained a slightly decreased yield of **3c** (entries 10 and 11). On the other hand, upon treatment with lithium diisopropylamide (LDA),[11] *exo*-**4c** was obtained as a major product (entries 12 and 13).

These improved reaction conditions (entry 5) were successfully applied to a reaction of **1** with other α,ω-dibromoalkanes **2**, giving the corresponding spironorcamphors **3** in moderate to good yields. Interestingly, **3b** was isolated in 52% yield as compared to 3% reported in the literature.[4] Although none of the monoalkylated product, 3-*exo*-(3-bromopropyl)norcamphor (*exo*-**4b**), was detected in the products, allylation[12] became a significant side reaction, a fact possibly attributable to the formation of allyl bromide by the ready dehydrobromination of **2b** compared to the other α,ω-dibromoalkanes. A mixture of allylated compounds, 3-*exo*-allylnorcamphor (*exo*-**5**, 7%),[11b,c] 3-*endo*-allylnorcamohor (*endo*-**5**, 4%), and 3,3-diallylnorcamphor (**6**, 1%) was isolated as by-products. Enol ether, which would be derived from *exo*-**4b** by intramolecular O-alkylation, was not observed.[13]

It is noteworthy that spiro[bicyclo[2.2.1]heptane-2,1′-cycloheptan]-3-one (**3e**) containing a seven-membered ring was produced in moderate yield, since the corresponding spirocyclohexanone has been obtained in only 8% yield from cycloalkylation of cyclohexanone with **2e**.[14] Although the preparation of a three-membered ring by alkylation is a kinetically favored process,[3a] we were not able to isolate the spiro[bicyclo[2.2.1]heptane-2,1′-cyclopropan]-3-one (**3a**).[15]

In conclusion, spironorcamphors (**3**) can now be easily obtained in good yields from the reaction of norcamphor (**1**) with α,ω-dibromoalkane (**2**) in the presence of $NaNH_2$. This ready availability should enhance the attractiveness of these compounds as starting materials for several reactions, including dehydration-rearrangement reactions.[1a,2b]

Experimental

Preparation of Spironorcamphors (3). General Procedure. To a magnetically stirred solution of norcamphor (**1**) (5.51 g, 50 mmol) and α,ω-dibromoalkane (**2**) (75 mmol) in dry Et_2O (150 ml) was added $NaNH_2$ (4.88 g, 125 mmol) in one portion. After being refluxed under a nitrogen atmosphere for 24 h, the reaction mixture was cooled to room temperature and poured into cold water (150 ml). The organic layer was separated, and the aqueous portion was extracted two times with Et_2O. The ethereal extracts were washed with a saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by column chromatography on silica gel using hexane–Et_2O (10:1) as an eluent afforded **3** as a colorless liquid.

Spiro[bicyclo[2.2.1]heptane-2,1′-cyclobutan]-3-one (3b): Yield 52%; IR (neat) 2975, 1750, 1465 cm^{-1}; ^1H NMR δ= 1.30—2.25 (m, 12H), 2.45—2.60 (m,2H); ^{13}C NMR δ=15.1 (t), 21.9 (t), 24.4 (t), 25.4 (t), 30.4 (t), 34.1 (t), 45.4 (d), 49.6 (d), 54.4 (s), 221.3 (s); MS *m/z* 150 (M^+), 122, 84, 81,67.

Capillary GLC analysis of the crude reaction mixture at 90 °C showed that 7% of 3-*exo*-allylnorcamphor (*exo*-**5**), 4% of 3-*endo*-allylnorcamphor (*endo*-5) and 1% of 3,3-diallylnorcamphor (**6**) were present as by-products. The mass spectrum and GLC retention time of *exo*-**5** were identical with those of an authentic sample, which was prepared by alkylation of **1** with allyl bromide in the presence of LDA. The other products, *endo*-**5** and **6**, isolated by preparative GLC, had the following properties:

***exo*-5**:[11b,c] IR (neat) 2975, 1755, 920 cm^{-1}; ^1H NMR δ=1.26—2.13 (m, 8H), 2.25—2.61 (m, 3H), 4.97—5.11 (m, 2H), 5.70—5.89 (m, 1H); ^{13}C NMR δ=23.9 (t), 28.0 (t), 33.3 (t), 34.6 (t), 38.5 (d), 49.6 (d), 53.2 (d), 116.1 (t), 136.4 (d), 219.0 (s); MS *m/z* 150 (M^+), 109, 81, 67, 41.

***endo*-5**: IR (neat) 2975, 1755, 920 cm^{-1}; ^1H NMR δ=1.32—2.18 (m, 8H), 2.43—2.67 (m, 3H), 4.97—5.11 (m, 2H), 5.70—5.89 (m, 1H); ^{13}C NMR δ=21.0 (t), 25.3 (t), 30.6 (t), 37.0 (t), 38.2 (d), 50.5 (d), 53.3 (d), 115.8 (t), 136.4 (d), 218.9 (s); MS *m/z* 150 (M^+), 109, 81, 67, 41; Found: *m/z*, 150.1039. Calcd for $C_{10}H_{14}O$: M, 150.1045

6: IR (neat) 3000, 1740, 920 cm^{-1}; ^1H NMR δ=1.40—2.71 (m, 12H), 4.95—5.23 (m, 4H), 5.72—5.96 (m, 2H); ^{13}C NMR δ=23.2 (t), 25.4 (t), 34.6 (t), 36.0 (t), 36.7 (t), 43.4 (d), 50.3 (d), 52.5 (s), 117.5 (t), 117.9 (t), 133.9 (d), 134.1 (d), 220.1 (s); MS *m/z* 190 (M^+), 93, 79, 67, 41; Found: *m/z*, 190.1350. Calcd for $C_{13}H_{18}O$: M, 190.1358.

Spiro[bicyclo[2.2.1]heptane-2,1′-cyclopentan]-3-one (3c): Yield 63%; IR (neat) 2980, 1750, 1470 cm^{-1}; ^1H NMR δ=1.30—2.00 (m, 14H), 2.24 (bs, 1H), 2.50—2.60 (m, 1H); ^{13}C NMR δ=23.9 (t), 25.5 (t), 26.4 (t), 26.8 (t), 32.7 (t), 36.0 (t), 36.4 (t), 46.5 (d), 49.8 (d), 59.0 (s), 223.9 (s); MS *m/z* 164 (M^+), 95, 68, 67, 41. Anal. ($C_{11}H_{16}O$) C, H.

Spiro[bicyclo[2.2.1]heptane-2,1′-cyclohexan]-3-one (3d): Yield 54%; IR (neat) 2950, 1750, 1455 cm^{-1}; ^1H NMR δ=1.10—2.00 (m, 16H), 2.40—2.70 (m, 2H); ^{13}C NMR δ=22.4 (t), 22.5 (t), 22.7 (t), 24.7 (t), 25.8 (t), 30.3 (t), 30.5 (t), 34.9 (t), 40.9 (d), 50.4 (d), 51.5 (s), 221.9 (s); MS *m/z* 178 (M^+), 109, 82, 67, 41. Anal. ($C_{12}H_{18}O$) C, H.

Spiro[bicyclo[2.2.1]heptane-2,1′-cycloheptan]-3-one (3e): Yield 48%; IR (neat) 2950, 1755, 1475 cm^{-1}; ^1H NMR δ=1.10—2.00 (m, 18H), 2.40—2.70 (m, 2H); ^{13}C NMR δ=23.0 (t), 24.1 (t), 24.5 (t), 25.4 (t), 29.2 (t), 29.3 (t), 32.7 (t), 33.5 (t), 34.7 (t), 43.6 (d), 50.1 (d), 53.5 (s), 223.1 (s); MS *m/z* 192 (M^+), 123, 81, 67, 55; Found: *m/z*, 192.1511. Calcd for $C_{13}H_{20}O$: M,192.1514.

Reaction of 1,4-Dibromobutane (2c) with Enolate Generated from 1 and $NaNH_2$ (Table 1, Entry 1). A variation of the procedure of Sauers et al.[4] was utilized. To a magnetically stirred solution of **1** (1.10 g, 10 mmol) and dodecane(0.85 g, 5 mmol; internal standard) in dry Et_2O (40 ml) was added $NaNH_2$ (1.17 g, 30 mmol) in one portion. After reflux under a nitrogen atmosphere for 4.5 h, the resulting mixture was poured onto **2c** (21.59 g, 100 mmol) and stirred at room temperature for 2 days. The reaction mixture was poured into cold water (50 ml), and the organic layer was separated. The aqueous portion was extracted two times with Et_2O. The combined organic extracts were washed with a saturated NaCl solution and dried over Na_2SO_4. A GLC analysis showed the presence of two major products [48% of **3c** and 31% of 3-*exo*-(4-bromobutyl)norcamphor (*exo*-**4c**)], which were purified by preparative GLC. *exo*-**4c**: IR (neat) 2975, 1750, 1470 cm^{-1}; ^1H NMR δ=1.10—2.08 (m, 13H), 2.35—2.70 (m, 2H, CH-CO-CH), 3.42 (t, J=6.6 Hz, 2H, CH_2Br); ^{13}C NMR δ=24.0 (t), 26.9 (t), 28.0 (t), 28.3 (t), 32.6 (t), 33.5 (t), 34.8 (t), 39.2 (d), 49.5 (d), 53.7 (d), 219.9 (s); MS *m/z* 246 (M^++2), 244 (M^+), 95, 82, 67, 41; Found: *m/z*, 244.0442. Calcd for $C_{11}H_{17}OBr$: M, 244.0462.

Reaction of 1 with 2c in the Presence of Potassium *t*-Butoxide (*t*-BuOK)[10] (Table 1, Entry 10). To a magnetically stirred solution of **1** (1.10 g, 10 mmol), **2c** (3.24 g, 15 mmol) and dodecane (0.85 g, 5 mmol; internal standard) in dry benzene (40 ml) was added *t*-BuOK (2.81 g, 25 mmol) in one portion. The resulting mixture was heated 3 h at reflux under a nitrogen atmosphere. Upon cooling to room temperature, the reaction mixture was poured into water (50 ml). The organic layer was separated and the aqueous portion was extracted two times with Et_2O. The combined organic extracts were washed with a saturated NaCl solution and dried over Na_2SO_4. A GLC analysis showed the presence of **3c** as the main product (53% yield).

Reaction of 1 with 2c in the Presence of Lithium Diisopropylamide (LDA)[11] (Table 1, Entry 12). A 1.6 M (1 M=1 mol dm^{-3}) hexane solution of butyllithium (7.8 ml, 12.5 mmol) was added to a stirred solution of diisopropylamine in dry THF (10 ml) at −78 °C. The solution was stirred at −78 °C for 1 h and at 0 °C for an additional 1 h, and again cooled to −78°C. To the resulting LDA solution was added dropwise a solution of **1** (0.55 g, 5 mmol) in dry THF (10 ml). After stirring for 1 h at −78 °C, a solution of **2c** (1.62 g, 7.5 mmol) in dry THF (5 ml) was added into the mixture. The reaction mixture was allowed to warm to 0 °C, stirred at that temperature for 1 h and at room temperature for 60 h, and then poured into water (50 ml). The mixture was extracted three times with Et_2O. The combined extracts were washed with saturated NaCl solution and dried over Na_2SO_4. GLC analysis of the solution indicated the formation of **3c** (8%) and *exo*-**4c** (33%).

Cyclization of *exo*-4c to 3c in the Presence of $NaNH_2$. To a magnetically stirred solution of *exo*-**4c** (0.50 g, 2.04 mmol) and dodecane (0.185 g, 1.08 mmol; internal standard) in dry ether (15 ml) was added $NaNH_2$ (0.12 g, 3.06 mmol) in one portion. The resulting mixture was refluxed under nitrogen for 24 h, allowed to cool, and then poured into water (50 ml). The organic layer was separated and the aqueous portion was extracted two times with Et_2O. The combined extracts were washed with saturated NaCl solution and dried over Na_2SO_4. A GLC analysis showed that **3c** was formed in 87% yield.

References

1) a) W. R. Dolbier, Jr., "Mechanisms of Molecular Migrations," ed by B. S. Thyagarajan, Wiley-Interscience, New York (1971), Vol. 3, p. 1; b) A. P. Krapcho, *Synthesis*, **1974**, 383; c) A. P. Krapcho, *Synthesis*, **1976**, 425; d) B. M. Trost and B. R. Adams, *J. Am. Chem. Soc.*, **105**, 4849 (1983); e) R. D. Bach and R. C. Klix, *J. Org. Chem.*, **50**, 5438 (1985).

2) a) N. Takaishi, Y. Inamoto, and K. Aigami, *Chem. Lett.*, **1979**, 803 and references cited therein; b) N. Takaishi, Y. Inamoto, and K. Aigami, *J. Org. Chem.*, **45**, 2254 (1980); c) Y. Fujikura, N. Takaishi, and Y. Inamoto, *Tetrahedron*, **37**, 4465 (1981); d) N. Takaishi, H. Takahashi, and Y. Inamoto, *Tetrahedron Lett.*, **26**, 2361 (1985).

3) a) H. O. House, "Modern Synthetic Reactions," 2nd ed, Benjamin, Inc., Menlo Park, CA, (1972), Chapter 9; b) R. M. Moriarity, C. C. Chien, and T. B. Adams, *J. Org. Chem.*, **44**, 2206 (1979).

4) R. R. Sauers and A. Shurpik, *J. Org. Chem.*, **32**, 3120 (1967).

5) a) J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107 (1970); b) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York (1972), p. 181.

6) a) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *J. Am. Chem. Soc.*, **84**, 2611 (1962); b) J.Wolinski, D. R. Dimmel, and T. W. Gibson, *J. Org. Chem.*, **32**, 2087 (1967).

7) No reaction intermediate has been isolated in the cycloalkylation of the other cyclic ketones with **2**.

8) The enolate from 3-*exo*-methylnorcamphor with LDA, when quenched with acetic acid, has afforded 3.5:1 mixture of endo and exo with endo predominating: X. Creary, F. Hudock, M. Keller, J. F. Kerwin, Jr., and J. P. Dinnocenzo, *J. Org. Chem.*, **42**, 409 (1977).

9) For similar procedures, see: a) J. M. Conia, *Rec. Chem. Prog.*, **24**, 43 (1963); b) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963); c) J. S. McConaghy, Jr. and J. J. Bloomfield, *J. Org. Chem.*, **33**, 3425 (1968).

10) M. Mousseron, R. Jacquier, and H. Christol, *Bull. Soc. Chim. Fr.*, **1957**, 346.

11) a) W. Kreiser and L. Janitschke, *Chem. Ber.*, **112**, 408 (1979); b) R. Bloch, *Tetrahedron Lett.*, **1979**, 3945; c) P. Barraclough, *Tetrahedron Lett.*, **21**, 1897 (1980); d) J. E. Baldwin and T. C. Barden, *J. Am. Chem. Soc.*, **105**, 6656 (1983).

12) Similar allylated ketone formations have been reported for the reaction of cyclohexanone with **2b** in the presence of *t*-BuOK, where no spiroketone was observed; see: Ref. 10.

13) Formation of enol ethers has been observed in the intramolecular alkylation of 2-(3-bromopropyl)cyclohexanone or 2-(3-bromopropyl)cyclopentanone with *t*-BuOK: S. J. Etheredge, *J. Org. Chem.*, **31**, 1990 (1966).

14) H. Christol, M. Mousseron, and F. Plenat, *Bull. Soc. Chim. Fr.*, **1959**, 543.

15) The spironorcamphor **3a** has been prepared by acid-catalyzed oxirane rearrangement: D. H. Aue and R. N. Reynolds, *J. Am. Chem. Soc.*, **95**, 2027 (1973).