method A from **1a** in 94% yield: mp 205.2–207.1 °C (lit.[9] mp 205–206 °C); IR 2233, 1631 cm^{-1}; ^1H NMR δ 2.11 (s, 3 H), 2.88 (m, 2 H), 3.61 (m, 2 H), 3.88 (s, 3 H), 3.93 (s, 3 H), 6.61 (s, 1 H), 7.08 (s, 1 H), 7.50 (m, 5 H); ^{13}C NMR δ 27.86, 29.28, 44.73, 54.50, 56.06, 56.29, 110.20, 111.23, 120.52, 126.06, 127.39, 128.73, 130.76, 135.69, 148.88, 149.27, 172.10. A sample made by alkylation of the anion of 2-benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was essentially identical as reported.[9]

2-Benzoyl-1-cyano-6,7-dimethoxy-1-(methylethyl)-1,2,3,4-tetrahydroisoquinoline (2b). This compound was produced by cyanoacylation method B from **1b** in 63% yield: mp 181.1–182.3 °C (EtOH); IR 2232, 1655 cm^{-1}; ^1H NMR δ 0.70 (d, 3 H), 1.19 (d, 3 H), 2.60 (dt, 1 H), 2.95 (dt, 1 H), 3.24 (dt, 1 H), 3.38 (m, 1 H), 3.88 (s, 3 H), 3.92 (s, 3 H), 4.00 (dt, 1 H), 6.63 (s, 1 H), 7.10 (s, 1 H), 7.47 (m, 5 H); ^{13}C NMR δ 16.33, 19.04, 29.59, 35.10, 45.89, 55.99, 56.18, 62.84, 111.15, 112.13, 119.34, 122.42, 126.95, 128.37, 128.75, 130.30, 136.57, 147.42, 149.07, 172.19. A sample was also prepared by alkylation of 2-benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[12] using a reported method;[10] its mp and spectral data were identical to the compound prepared by cyanoacylation. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64. Found: C, 72.39; H, 6.64.

Attempted Cyanoacylation of 6,7-Dimethoxy-1-(3′,4′-dimethoxybenzyl)-3,4-dihydroisoquinoline. The reaction (method B) of **1c** gave a quantitative yield of the elimination product **3** as white needle crystals from ethyl acetate: mp 222.5–223.3 °C; IR 3005, 2934, 2912, 2885, 2883, 1640 cm^{-1}; ^1H NMR δ 2.86 (m, 1 H), 3.31 (m, 2 H), 3.76 (s, 3 H), 3.86 (s, 3 H), 3.91 (s, 3 H), 3.94 (s, 3 H), 5.12 (m, 1 H), 6.35 (d, 2 H), 6.56 (d, 1 H), 6.70 (m, 2 H), 6.86 (d, 2 H), 7.01 (m, 3 H), 7.17 (m, 1 H); ^{13}C NMR δ 28.85, 42.21, 55.68, 55.83, 56.30, 106.72, 111.65, 112.17, 118.26, 121.07, 125.69, 126.62, 127.17, 127.61, 128.34, 129.12, 134.99, 135.85, 148.18, 148.32, 149.83, 150.06, 169.20. Anal. Calcd for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 73.07; H, 6.22; N, 3.20.

2-Benzoyl-1-cyano-6,7-dimethoxy-1-(3′,4′-dimethoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline (2d). This new compound was prepared from **1d** by cyanoacylation method B in quantitative yield: mp 219.2–220.7 °C (toluene); IR 2234, 1683, 1646 cm^{-1}; ^1H NMR δ 3.00 (d, 1 H), 3.56 (m, 2 H), 3.79 (s, 3 H), 3.81 (s, 6 H), 3.90 (s, 3 H), 4.27 (dt, 1 H), 6.76 (d, 1 H), 6.83 (s, 1 H), 6.97 (s, 1 H), 7.42 (m, 7 H); ^{13}C NMR δ 28.32, 45.04, 55.83, 55.98, 109.42, 109.75, 112.09, 117.55, 119.67, 122.16, 125.76, 126.30, 127.16, 128.02, 128.65, 131.15, 133.49, 148.65, 149.04, 150.29, 152.95, 172.33, 188.19. Anal. Calcd for $C_{28}H_{26}N_2O_6$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.94; H, 5.43; N, 5.70.

1-Methylisoquinoline (4a). Compound **5a**[11] (1.25 g, 4.56 mmol) was refluxed for 6 h with potassium hydroxide (0.54 g, 9.59 mmol) in 95% ethanol (30 mL) and water (4 mL). To the cooled amber solution was added 15 mL of water. The solution was extracted with dichloromethane, and the organic phase was washed with water and then brine. The organic phase was dried over anhydrous sodium sulfate and then evaporated to give 0.65 g of a yellow oil: quantitative yield; IR (neat) 3051, 2993, 2967, 2920, 2863 cm^{-1}; ^1H NMR δ 2.95 (s, 3 H), 7.50 (d, 1 H), 7.57 (t, 1 H), 7.66 (t, 1 H), 7.80 (d, 1 H), 8.11 (d, 1 H), 8.40 (d, 1 H); ^{13}C NMR δ 22.00, 118.96, 125.29, 126.70, 126.86, 127.25, 129.59, 141.47.

2-Benzoyl-1-cyano-1-methyl-1,2-dihydroisoquinoline (5a). This compound was made by cyanoacylation (method A) of **4a** and purified by flash chromatography and subsequent recrystallization from ethanol in 56% yield: mp 123.6–125.2 °C (lit.[11] mp 119–121 °C); IR 2237, 1662 cm^{-1}; ^1H NMR δ 2.00 (s, 3 H), 5.77 (d, 1 H), 6.46 (d, 1 H), 7.10 (m, 1 H), 7.55 (m, 8 H); ^{13}C NMR δ 26.52, 57.00, 106.62, 118.72, 125.19, 125.91, 128.34, 128.58, 129.27, 129.43, 131.08, 131.93, 133.26, 169.35. A sample made by alkylation[10] of 2-benzoyl-1-cyano-1,2-dihydroisoquinoline[2] was identical.

1-Benzylisoquinoline (4b). This compound was made from **5b**[10] by the method given for **4a** as a yellow oil in 91% yield: IR (neat) 3084, 3053, 3027 cm^{-1}; ^1H NMR δ 4.69 (s, 2 H), 7.26 (m, 5 H), 7.55 (m, 3 H), 7.81 (d, 1 H), 8.15 (d, 1 H), 8.51 (d, 1 H); ^{13}C NMR δ 42.00, 119.67, 125.76, 126.20, 127.09, 127.32, 128.43, 128.56, 129.75, 136.62, 139.44, 142.01, 160.14.

2-Benzoyl-1-cyano-1-benzyl-1,2-dihydroisoquinoline (5b). Prepared by cyanoacylation method B from **4b**, the yield of **5b** was 85%: mp 133.6–135.0 °C (lit.[10] mp 123.5–125.0 °C); IR 2235, 1667 cm^{-1}; ^1H NMR δ 3.54 (d, J = 13 Hz, 1 H), 3.74 (d, J = 13 Hz, 1 H), 5.54 (d, J = 8 Hz, 1 H), 6.35 (d, J = 8 Hz, 1 H), 6.81 (d, 2 H), 7.04 (d, 1 H), 7.01 (m, 1 H), 7.21 (m, 5 H), 7.51 (m, 3 H), 7.61 (m, 2 H); ^{13}C NMR δ 43.64, 61.45, 106.54, 117.75, 124.82, 126.54, 127.54, 127.79, 127.95, 128.73, 129.20, 129.50, 130.99, 131.85, 133.18, 133.49, 169.51. A sample made in 56% yield by alkylation of 2-benzoyl-1-cyano-1,2-dihydroisoquinoline[2] according to the literature[10] was identical.

Registry No. **1a**, 4721-98-6; **1b**, 58735-47-0; **1c**, 6957-27-3; **1d**, 20345-69-1; **2a**, 73154-69-5; **2b**, 137465-61-3; **2d**, 137465-62-4; **3**, 137465-63-5; **4a**, 1721-93-3; **4b**, 6907-59-1; **5a**, 16576-32-2; **5b**, 16576-35-5; TMSCN, 7677-24-9; PhCOCl, 98-88-4; 2-benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 10174-83-1; 2-benzoyl-1-cyano-1,2-dihydroisoquinoline, 844-25-7.

(9) Coutts, I. G. C.; Hamblin, M. R.; Tinley, E. J.; Bobbitt, J. M. *J. Chem. Soc., Perkin Trans 1*, **1979**, 2744–2750.
(10) Gibson, H. W. *J. Heterocycl. Chem.* **1970**, *7*, 1169–1172.
(11) Boekelheide, V.; Weinstock, J. *J. Am. Chem. Soc.* **1952**, *74*, 660–663.
(12) Gibson, H. W.; Popp, F. D. *J. Chem. Soc. C* **1966**, 1860–1864.

One-Step Synthesis of Substituted 6,8-Dioxabicyclo[3.2.1]octanes: Easy Preparation of Racemic Frontalin, Brevicomins, and Related Systems

Miguel Yus* and Diego J. Ramón

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apartado 99, 03080 Alicante, Spain

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Substituted 6,8-dioxabicyclo[3.2.1]octanes are important beetle aggregation pheromones,[1] and their biological activity in racemic or enantiomeric form is pertinent to the protection of ecologically important coniferous forests.[2] In general, the activity of both enantiomers is different; nevertheless, the racemic mixtures are sufficiently potent for their practical application.[3] From this family of compounds, frontalin[4] and brevicomins[5] are the best known, and numerous syntheses for both and related molecules have been reported.[6] However, in general, their preparation takes place through a multistep process and the procedures are rarely of general use. On the other hand, we have recently described the preparation and reactivity[7] of masked lithium bishomoenolates of the type **1**, which are easily prepared from the corresponding chlorinated precursors by stoichiometric[7] or catalytic[8] lithiation at low temperature. In this paper, we report the one-step preparation of the bicyclic skeleton of the frontalin type by direct reaction of intermediates **1** with protected 2-hydroxy carbonyl compounds.

The reaction of the lithiated ketal **1a**[7] (prepared by lithiation of 2-(3-chloropropyl)-1,3-dioxolane with lithium

(1) (a) Borden, J. H. Aggregation Phermones. In *Comprehensive Insect Physiology, Biochemistry and Pharmacology*; Kerkut, G. A., Gilberts, L. I., Eds.; Pergamon Press: Oxford, 1985; Vol. 9, p 257. (b) Payne, T. L.; Andryszak, N. A.; Wieser, H.; Dixon, E. A.; Ibrahim, N.; Coers, J. *J. Chem. Ecol.* **1988**, *14*, 1217.
(2) Oehlschlager, A. C.; Johnston, B. D. *J. Org. Chem.* **1987**, *52*, 940.
(3) Joshi, N. N.; Mamdapur, V. R.; Chadha, M. S. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2963.
(4) Sugai, T.; Kakuya, H.; Ohta, H. *J. Org. Chem.* **1990**, *55*, 4643.
(5) (a) Achmatowicz, B.; Wicha, J. *Liebigs Ann. Chem.* **1988**, 1135. (b) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100. (c) Matsumoto, K.; Suzuki, N.; Ohta, H. *Tetrahedron Lett.* **1990**, *31*, 7163.
(6) (a) Mulzer, J. *Nach. Chem. Tech. Lab.* **1984**, *32*, 798. (b) Ibrahim, N.; Eggimann, T.; Dixon, E. A.; Wieser, H. *Tetrahedron* **1990**, *46*, 1503.
(7) (a) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1990**, *31*, 3763, 3767. (b) Ramón, D. J.; Yus, M. *J. Org. Chem.* **1991**, *56*, 3825.
(8) Yus, M.; Ramón, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 398.

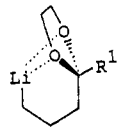
0022-3263/92/1957-0750$03.00/0

Table I. Preparation of Substituted 6,8-Dioxabicyclo[3.2.1]octanes

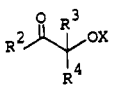
entry	starting materials	product[a] no.	yield[b] (%)
1	1a + 2a	3a	61
2	1a + 2b	3b	53
3	1b + 2a	3c	68
4	1b + 2b	3d	71
5	1b + 2c	3e	40
6	1b + 2d	3f + 3g[c]	42

[a] All isolated products were >95% pure (GLC and 300 MHz ^{1}H NMR). [b] Isolated yield after column chromatography (basic aluminum oxide; hexane/diethyl ether) based on the chloroketal precursor of the masked lithium bishomoenolate 1. [c] Endo/exo ratio = 1/1.2 from GLC and 75-MHz ^{13}C NMR; see also ref 13.

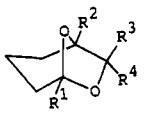
powder in the presence of a catalytic amount (1%) of naphthalene[8] at −78 °C) with [(trimethylsilyl)oxy]acetone **2a** at −78 °C to +20 °C and further hydrolysis with 2 N hydrochloric acid gave directly the corresponding product **3a**. The same process but using **2b** as electrophile instead of **2a** gave **3b**. When the starting lithium bishomoenolate was **1b** the reaction with **2a** or **2b** under the same reaction conditions yielded the expected bicycles frontalin (**3c**) or **3d**, respectively (Table I, entries 1–4). All these reactions were first tried using the corresponding alcoholates of the unprotected hydroxy carbonyl compounds, but the yields were poor. However, in the case of the substrate **2c** the same procedure as above with the intermediate **1b** gave the expected product **3e** in moderate yield (Table I, entry 5).[9] Finally, we applied the described methodology for the preparation of *endo/exo*-brevicomin: in this case it was necessary to use 2-(benzyloxy)butanal in order to get the expected reaction with the organolithium compound **1b**. After extractive workup the benzylated intermediate was deprotected with hydrogen and palladium–carbon in ethyl acetate, and the final acid hydrolysis yielded the expected mixture of *endo*- and *exo*-brevicomin (**3f** and **3g** in a 1:1.1 molar ratio; Table I, entry 6).



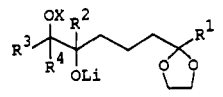
1a; R^1 = H
b; R^1 = Me



2a; R^2 = Me, R^3 = R^4 = H, X = $SiMe_3$
b; R^2 = Et, R^3 = R^4 = H, X = $SiMe_3$
c; R^2 = Me, R^3 = R^4 = Me, X = Li
d; R^2 = R^3 = H, R^4 = Et, X = $PhCH_2$



3a; R^1 = H, R^2 = Me, R^3 = R^4 = H
b; R^1 = H, R^2 = Et, R^3 = R^4 = H
c; R^1 = R^2 = Me, R^3 = R^4 = H
d; R^1 = Me, R^2 = Et, R^3 = R^4 = H
e; R^1 = R^2 = R^3 = R^4 = Me
f; R^1 = Me, R^2 = R^3 = H, R^4 = Et
g; R^1 = Me, R^2 = H, R^3 = Et, R^4 = H



4

From a mechanistic point of view it is clear that the first reaction product is of the type **4**, which after deprotection suffers spontaneous cyclization to give the obtained dioxabicycles **3**.

From the results described in this paper we conclude that this methodology is a convenient route for the one-step construction of the frontalin-type skeleton. Studies are under way in order to prepare chiral bicyclic systems of the type **3** by using chiral lithium ketals or/and chiral hydroxy carbonyl compounds.

Experimental Section[10]

General Procedure for the Preparation of Substituted 6,8-Dioxabicyclo[3.2.1]octane 3. To a suspension of lithium powder (Aldrich, 14 mmol) and naphthalene (0.025 mmol) in THF (5 mL) was added the corresponding chloroketal (2.5 mmol) at −78 °C under argon, and it was stirred for 1 h at the same temperature. To the resulting mixture was added the corresponding electrophile **2** (2.5 mmol), and it was stirred overnight allowing the temperature to rise to 20 °C. Then, it was acidified with 2 N HCl, stirred for 1 h, and extracted with diethyl ether (2 × 10 mL), and the organic layer was dried over Na_2SO_4 and carefully evaporated (*ca.* 100 Torr). The resulting residue was purified by column chromatography (basic aluminum oxide; hexane/diethyl ether) to yield products **3**. In the case of using **2d** as electrophile, the crude extract after the reaction was debenzylated by standard catalytic hydrogenation (H_2 (1 atm)/10% Pd–C (100 mg) in ethyl acetate (50 mL)) before the final acid treatment as above. Yields are reported in Table I. Physical and spectral data follow. In the case of the known compounds **3a**,[1b] **3c**,[4] and **3f/3g**,[5b] their data are in agreement with those reported in the literature and are included as supplementary material.

1-Ethyl-6,8-dioxabicyclo[3.2.1]octane (3b): R_f = 0.63 (hexane/ethyl acetate = 4/1); bp 120 °C (100 Torr) (Kugelrohr); IR (film) 1100, 1000 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7.55 Hz, 3 H, CH_3), 1.40–2.10 (m, 6 H, $(CH_2)_3$), 3.43, 3.91 (2 d, J = 6.8 Hz, 2 H, CH_2O), 5.45–5.60 (m, 1 H, OCHO); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.25, 16.55, 29.55, 30.85, 31.9, 72.0, 81.5, 102.75; MS 143 (M^+ + 1, 5), 142 (M^+, 56), 112 (32), 85 (42), 71 (53), 68 (100), 67 (60), 57 (86), 41 (42).

1-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (3d): R_f = 0.70 (hexane/ethyl acetate = 4/1); bp 125 °C (100 Torr) (Kugelrohr); IR (film) 1110, 1030 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J = 7.35 Hz, 3 H, CH_2CH_3), 1.42 (s, 3 H, CCH_3), 1.45–2.0 (m, 6 H, $(CH_2)_3$), 3.50, 3.88 (2 d, J = 6.45 Hz, 2 H, CH_2O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.2, 17.8, 24.6, 29.75, 31.1, 34.85, 72.75, 82.65, 108.0; MS 157 (M^+ + 1, 2), 156 (M^+, 14), 144 (44), 86 (63), 68 (35), 43 (100).

1,5,7,7-Tetramethyl-6,8-dioxabicyclo[3.2.1]octane (3e): R_f = 0.70 (hexane/ethyl acetate = 4/1); IR (film) 1180, 1090 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16, 1.20 (2 s, 6 H, $C(CH_3)_2$), 1.33 (s, 3 H, CH_3CO), 1.41 (s, 3 H, CH_3CO_2), 1.45–2.05 (m, 6 H, $(CH_2)_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.25, 20.6, 21.2, 25.95, 26.95, 31.8, 33.45, 82.5, 82.55, 105.55; MS 170 (M^+, 2), 112 (31), 43 (100).

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Registry No. 1a, 129471-18-7; **1b**, 133549-41-4; **2a**, 26205-43-6; **2b**, 131340-64-2; **2c**, 137720-38-8; **2d**, 137819-87-5; **3a**, 137720-39-9; **3b**, 137720-40-2; **3d**, 137720-41-3; **3e**, 137720-42-4; **3f**, 62532-53-0; **3g**, 60018-04-4.

Supplementary Material Available: Physical and spectral data for the known compounds **3a**,[1b] **3c**,[4] and **3f/3g**;[5b] ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR of compounds **3b**, **3d**, and **3e** (7 pages). Ordering information is given on any current masthead page.

(9) It was not possible to obtain 3-methyl-3-(trimethylsilyloxy)-butan-2-one by the same procedure as for **2a** and **2b** (see Experimental Section).

(10) For general information see reference 7b. Hydroxy carbonyl compounds precursors of starting materials **2** were commercially available (Aldrich). Compounds **2a** and **2b** were prepared (90–95%) by silylation of the corresponding hydroxy ketones (Et_3N, Me_3SiCl in THF).[11] Deprotonation of 3-hydroxy-3-methylbutanone to give **2c** was carried out in situ with butyllithium at −78 °C in THF. Compound **2d** was prepared according to the described method.[12]

(11) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.
(12) Bianchi, D.; Cesti, P.; Golini, P. *Tetrahedron* **1989**, *45*, 869.
(13) Both endo/exo diastereomers showed the same R_f value.