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Improvement of a Lineatin Synthesis

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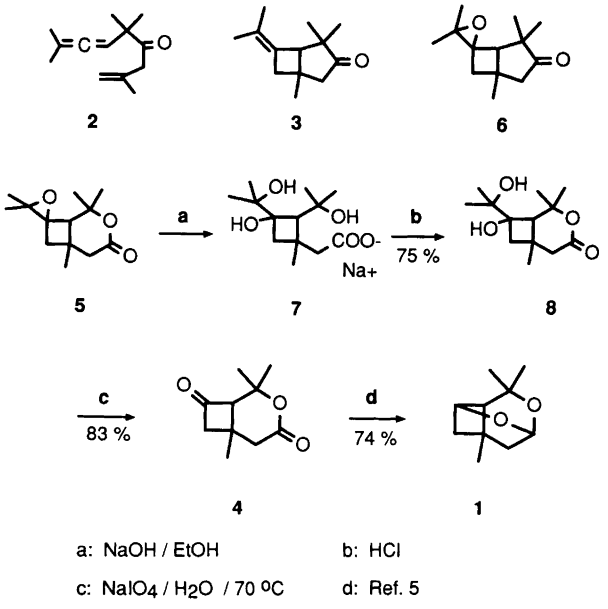
An improvement of the Skattebøl synthesis of the aggregation pheromone of the ambrosia beetle, *Trypodendron lineatum* (L), has been accomplished by oxidative cleavage of a glycolic key intermediate.

The ambrosia beetle, *Trypodendron lineatum* (L) is a serious pest in the coniferous forests of the entire northern hemisphere. An aggregation pheromone, lineatin, with the structure **1**, was isolated[1] and later synthesized by Borden and co-workers.[2] Since then a number of groups have reported synthesis of lineatin, using a variety of synthetic schemes.[3] The method described by Skattebøl and Stenstrøm[4] is the most efficient so far reported.



Scheme 1.

Starting from the allenic vinyl ketone **2** (Scheme 1), the Skattebøl synthesis was reported to produce **1** in six steps in 27% overall yield.[4] Ring closure of **2** gave **3**, which was further transformed into the keto-lactone **4** via the epoxide **5**. However, a drawback of this method, when performed by us on a multimolar scale, was that yields of **4** rarely exceeded 15–30%. Formation of a number of inseparable impurities was also associated with this route. We have, therefore, studied alternative methods for producing **4**. Our findings are reported here.

Results and discussion

The transformation of **2** into **3** was performed according to the literature procedure.[4] The Baeyer–Villiger/epoxidation reaction of **3** with MCPBA was sensitive to the reaction conditions and yielded varying amounts of the desired product **5** together with the by-product **6**. The epoxy lactone **5** was obtained in an essentially quantitative yield of 94% purity when the reaction was performed in dichloromethane with 3 mol equiv. of MCPBA in the presence of anhydrous sodium carbonate. The anhydrous conditions were first believed to cause the increased selectivity. However, in the presence of molecular sieves (3 Å) **6** was formed as almost the exclusive product, (4% **5** and 87% **6**). Addition of water or anhydrous alumina had similar effects favoring formation of **6**.

Crude **5** was used in subsequent steps without further purification, but was also distilled under reduced pressure (b.p. 80°C at 0.15 mmHg) to yield 54% of the product of 98% purity. Spectroscopic properties were in agreement with those of an authentic sample.

The modified method leading to **4** included an initial ring opening of the epoxide **5** by NaOH in ethanol. The product formed in this reaction was the carboxylate **7**. Neutral impurities were removed from an aqueous solution of **7** by extraction with ether or hexane. Acidification of the aqueous solution with hydrochloric acid followed by extraction with ether, gave 75% of pure **8** (>98% by GLC) as a white crystalline product (m.p. 152–155°C). NMR and GLC data for this product clearly indicated a mixture of two isomers. An obvious advantage of this strategy is that the synthetic intermediate **8** can be isolated in a satisfactory yield and in high purity.

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Conversion of **8** into the keto lactone **4** was next achieved by treatment of **8** with sodium metaperiodate in water at 70°C. This gave 83% of pure **4** (>99% by GLC) as a white crystalline solid with m.p. 95–96°C. Spectroscopic properties were in agreement with those of an authentic sample. Finally, **4** was converted into **1** (>98% by GLC) in 74% yield using known procedures.[5]

Experimental

The GLC measurements were performed on a VARIAN 3700 gas chromatograph equipped with a BP-5 capillary column. GC–MS analysis were performed with a Hewlett Packard 5985A GC/MS System. Mass spectra were recorded on an AEI MS 902 mass spectrometer. IR spectra were recorded on a Beckman IR 4200 infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Jeol JNM-FX100 Fourier Transform NMR spectrometer. Melting points are uncorrected.

The starting material, 6-isopropylidene-1,4,4-trimethylbicyclo[3.2.0]heptan-3-one, **3**, (75% purity by GLC), and reference materials were provided by Borregaard Fine Chemicals.

2,2,3',3',6-Pentamethyl-3-oxaspiro{bicyclo[4.2.0]octane-8,2'-oxiran}-4-one **5**. To a solution of **3** (5.0 g, 26 mmol) in CH_2Cl_2 (200 ml) was added a mixture of *m*-chloroperbenzoic acid (14 g, 75 mmol) and Na_2CO_3 (7.1 g, 67 mmol) in portions and the reaction was stirred overnight at room temperature. To the reaction mixture were then added 200 ml of an aqueous $Na_2S_2O_3$ solution (10%) and stirring was continued for another 3 h. After separation of the organic layer the aqueous layer was extracted twice with CH_2Cl_2 (100 ml). The combined organic layers were washed with saturated, aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. This gave a quantitative yield of **5** (94% pure by GLC) as an orange oil, which was used without further purification. GLC analysis indicated an approx. 1:1 mixture of isomers, probably the *exo* and *endo* products.

Distillation of 1.17 g of crude **5** using a short-path distillation apparatus (b.p. 80°C, 0.15 mmHg) yielded 0.64 g of the product (98%) as a pale yellow oil, which was identified on the basis of the spectroscopic properties.

MS [*m/z* (% rel. int.)]: 224 ($M^{\pm}$, 1), 209 (1), 166 (19), 151 (6), 139 (12), 124 (81), 109 (44), 107 (43), 96 (100), 83 (34). IR: (neat) 2990, 2970, 2930, 2875, 1735, 1463, 1445, 1433, 1388, 1375, 1330, 1303, 1285, 1257, 1214, 1190, 1150, 1125, 1110, 1090, 1075, 980, 955, 910, 885, 848, 810, 745, 675. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11 (s, 3 H), 1.33 (s, 3 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.44 (s, 3 H), 1.73 (d, *J* 3.8 Hz) and 1.78 (d, *J* 3.8 Hz) (1H), 2.50 and 2.55 (AB, *J* 16.9 Hz, 2 H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 20.7, 23.7, 27.7, 28.1, 29.9, 32.5, 40.7, 42.5, 32.5, 60.3, 68.3, 81.1, 171.2.

8-Hydroxy-8-(1-hydroxy-1-methylethyl)-2,2,6-trimethyl-3-oxabicyclo[4.2.0]octan-4-one, **8**. To a solution of **5** (1.0 g, 4.5 mmol) in ethanol (96%, 40 ml) was added aqueous NaOH (1 M) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and then water (60 ml) was added. This aqueous solution was extracted with ether. The aqueous phase was acidified with HCl (1 M) and then subjected to continuous extraction with ether. This ether extract was dried over anhydrous magnesium sulfate and filtered. The ether was removed under reduced pressure yielding 0.85 g, 3.5 mmol, 77% of **8** as a pale yellow product (98% purity by GLC).

The product **8**, m.p. 152–155°C, exhibited the following spectroscopic properties.

MS [*m/z* (% rel. int.)]: 242 ($M^{\pm}$, 1), 224 (1), 209 (1), 183 (6), 169 (7), 156 (36), 141 (45), 125 (39), 123 (22), 109 (6), 99 (23), 97 (27), 96 (45), 95 (25), 83 (52). IR (KBr): 3460, 3420, 3240, 2985, 2980, 2975, 2720, 2620, 2520, 1710, 1480, 1465, 1455, 1405, 1370, 1328, 1320, 1295, 1275, 1230, 1195, 1180, 1152, 1135, 1120, 1108, 1070, 990, 975, 950, 925, 900, 855, 840, 825, 790, 690 cm^{-1}. ^{1}H NMR (100 MHz, CD_3OD): δ 1.13 (s, 3 H), 1.20 (s, 3 H), 1.27 (s, 3 H), 1.33 (s, 3 H), 1.90 and 2.15 (AB *J* 13.0 Hz, 2 H), 2.26 (s, 1H), 2.65 (d, *J* 16 Hz), 3.45 (d, *J* 16 Hz). ^{13}C NMR (25 MHz, CD_3OD): δ 24.2, 25.2, 28.7, 32.5, 30.7, 35.9, 42.4, 56.6, 73.6, 74.0, 83.0, 176.4.

2,2,6-Trimethyl-3-oxabicyclo[4.2.0]octane-4,8-dione, **4**. To a solution of **8** (740 mg, 3.1 mmol) in H_2O (30 ml) was added $NaIO_4$ (2.62 g, 12.2 mmol) in portions and the mixture was stirred overnight in an oil bath at 70°C. The reaction mixture was extracted with ether (4 × 20 ml). The combined ether extracts were then washed with brine (30 ml) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. This yielded 0.47 g, 2.6 mmol, 83% of an off-white solid material (purity >99% by GLC) with m.p. 95–96°C. The spectroscopic properties were in accordance with the literature.[4]

3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane, lineatin, **1**. A solution of **4** (480 mg, 2.6 mmol) in dry ether (11 ml) was cooled to −70°C in a dry ice–acetone bath. DIBAL (1.0 M in hexane, 6 ml, 6 mmol) was added dropwise and the reaction mixture was stirred for 2 h. The mixture was then warmed to 0°C during the addition of saturated NH_4Cl solution (11 ml), and was then acidified with HCl (4 M). The reaction was stirred for 1 h after which the aqueous phase was separated and extracted with ether (4 × 10 ml). The combined ether layers were washed with saturated sodium bicarbonate solution. Distillation of the reaction mixture yielded 74% of the desired product as a clear liquid (98% pure by GLC). The spectroscopic data were in agreement with those previously reported and of an authentic sample.[4]

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References

1. MacCennel, J. G., Borden, J. H., Silverstein, R. M. and Stohkink, E. *J. Chem. Ecol. 3* (1977) 549.
2. Borden, J. H., Handley, J. R., Johnston, B. D., MacConnel, J. G., Silverstein, R. M., Slessor, K. M., Swigar, A. A. and Wong, D. T. V. *J. Chem. Ecol. 5* (1979) 681.
3. Mori, K. In: ApSimon, J., Ed., *The Total Synthesis of Natural Products*, Wiley, NY, 1990, p. 436.
4. Skattebøl, L. and Stenstrøm, Y. *Acta Chem. Scand., Ser. B 39* (1985) 291.
5. Mori, K. and Sasaki, M. *Tetrahedron 36* (1980) 2197.

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