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IMPROVED SYNTHESIS OF 2,6,6-TRIMETHYL-1-CYCLOHEXENE-1-ACETALDEHYDE, A KEY INTERMEDIATE FOR DRIMANE-RELATED SESQUITERPENES.

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ABSTRACT: The titel compound is conveniently prepared in 65% overall yield by a two step synthesis starting from the commercially available β -ionone.

In the search for safer and more effective crop protecting agents the insect antifeedants hold a promising position.

Recently there has been increasing interest in the synthesis of many drimane sesquiterpenes, e.g. drimanin 1, cinnamolide 2, polygodial 3, and warburganal 4².

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An especially attractive strategy for the synthesis of these compounds is to use a Diels-Alder reaction for constructing the appropriate decalin skeleton. In most cases the reaction between 1,3,3-trimethyl-2-vinyl-1-cyclohexene and dimethylacetylenedicarboxylate was used for this purpose^{2a-2c}.

For the synthesis of more functionalized decalines Snowden³ used a substituted diene 12 which was reacted with dimethyl fumarate in refluxing xylene to give the cycloadduct in more than 95% yield. The synthesis of the diene starts from aldehyde 9. In most cases this aldehyde is synthesized by addition of acetylene to 2,2,6-trimethylcyclohexene^{2b} followed by a rearrangement of the adduct with $(\text{Ph}_3\text{SiO})_3\text{VO}^{2c}$.

Besides the development of synthetic strategies to the drimane sesquiterpene skeleton, the asymmetric synthesis of natural drimane type sesquiterpenes is an important goal. This is emphasized by the limited number of routes to these optically active drimane sesquiterpenes and the phytotoxicity associated with the racemates in some cases¹.

As part of our enantioselective Diels-Alder approach to optically active drimane sesquiterpenes we needed an efficient route to 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde 9. We hereby wish to report two new routes to aldehyde 9, the first one via an one carbon chain

scheme 1

a) 1. $\text{C}_6\text{H}_5\text{NH}_2$ 2. conc. H_2SO_4 , -20°C 3. KOH , CH_3OH , 0°C
 b) O_3 , CH_3OH , -40°C c) $(\text{CH}_3)_3\text{SiCH}_2\text{OCH}_3$, $s\text{-BuLi}$, -25°C d)
 90% HCOOH , 10 min.

extension from aldehyde **7** and the second one using an one carbon chain shortening starting from carboxylic acid **10**. Especially the second route is a considerable improvement as compared to current syntheses of aldehyde **9** and as a consequence of the important dienes such as **12**.

Our first synthesis of the desired aldehyde **9** starts with cyclocitral **7** (scheme 1). This aldehyde can either be synthesized from citral **5** by means of cyclization in concentrated sulfuric acid⁴, or by ozonolysis from β -ionone **6**^{2c}. By reaction of **7** with methoxy(trimethylsilyl)methylolithium^{5,6} the carbon chain was extended with one carbon atom to silyl compound **8**⁷. Treatment of the adduct with 90% aqueous formic acid gave aldehyde **9**⁷. But because of the low yield of this reaction and

scheme 2

a) NaOH, Br₂ b) DPPA, dioxane c) 0.5 N HCl, dioxane, reflux d) pyrrolidine, C₆H₅CH₃, 60°C

the fact that the starting materials, aldehyde **7** and methoxy(trimethylsilyl)methyl lithium, had to be synthesized we searched for a better route which could be carried out on a large scale and in which the starting materials were commercially available.

The second synthesis of **9** starts from the commercially available β -ionone (scheme 2). This compound was oxidized with sodium hypobromite to the carboxylic acid **10** in 95% yield (lit. 90%)^{2d}. In most cases the carboxylic acid could be used without further purification. Treatment of the carboxylic acid with one equivaleant diphenyl phosphoryl azide (DPPA)¹² afforded the corresponding acyl azide **11**, which was converted, without isolation or purification, into the desired aldehyde **9**, via a Curtius rearrangement in a refluxing

0.5 N HCl, dioxane solution. Pure 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde 9 was obtained in 71% yield. In all respects identical with an independantly prepared sample. The reaction between the aldehyde 9 and pyrrolidine gave, according to the procedure of Snowden³, the dieneamine 12 in 88% yield (lit 96%).

The two step route to aldehyde 9 from β -ionone in 65% overall yield is operationally simple. The advantages of this new two step route to aldehyde 9 are the facile experimental procedures, the use of β -ionone as a cheap starting material and the fact that it gives readily access to multigram quantities of functionalized dienes (such as 12) which are considered as attractive drimane precursors.

Experimental section

α -[methoxy(trimethylsilyl)methyl]-2,6,6-trimethyl-1-cyclohexenemethanol (8)

A solution of 6.80 g (57.6 mmol) methoxymethyltrimethylsilane in 50 ml dry THF was treated with 45 ml *s*-butyllithium (1.3 M in hexane) at -70°C, followed by warming to -25°C. After addition of 8.00 g (52.6 mmol) cyclocitral, stirring was continued at -25°C for 1/2 h. 100 ml Water was added and the resulting mixture was extracted with ether (3 x 50 ml). The combined organic layers were washed with brine and dried on MgSO₄. After filtration and evaporation of the solvent the product was purified by bulb-to-bulb distillation (110°C, 0.1 mm Hg) yielding 12.8 g (90%) of a slightly yellow oil. Major isomer; ¹H NMR (CDCl₃, 300 MHz): δ 0.10 (s, 9H), 1.02 (s, 3H), 1.09 (s, 1H), 1.42 (m, 2H), 1.58 (m, 2H), 1.90 (s, 3H), 1.96 (m, 2H), 3.17 (d, J = 7.0 Hz, 1H), 3.43 (s, 3H), 4.36 (m, 1H). ¹³C NMR (CDCl₃): δ -2.25 (q), 19.15 (t), 21.93 (q), 28.58 (q), 28.98 (q), 34.32 (t), 34.81 (s), 40.02 (t), 61.97 (q), 72.96 (d), 81.53 (d), 132.50 (s), 137.02 (s).

Minor isomer; ^1H NMR (CDCl_3 , 300 MHz): δ 0.13 (s, 9H), 1.03 (s, 3H), 1.10 (s, 3H), 1.42 (m, 2H), 1.58 (m, 2H), 1.85 (s, 3H), 1.96 (m, 2H), 3.24 (s, 3H), 3.40 (d, J = 7.2 Hz, 1H), 4.36 (m, 1H). ^{13}C NMR (CDCl_3): δ -2.67 (q), 19.30 (t), 21.22 (q), 27.60 (q), 29.10 (q), 33.95 (s), 34.10 (t), 40.09 (t), 60.57 (q), 71.28 (d), 78.91 (d), 131.80 (s), 141.87 (s).

2, 6, 6-Trimethyl-1-cyclohexene-1-acetaldehyde (9)

5.00 g (18.52 mmol) 8 was stirred at room temperature for 10 min in 25 ml 90% aqueous formic acid. This solution was then poured very carefully in 250 ml saturated NaHCO_3 and extracted with ether (2 x 100 ml). The combined organic layers were washed with saturated NaHCO_3 , dried on Na_2CO_3 and evaporated under reduced pressure yielding a yellow oil. After bulb-to-bulb distillation (140°C, 12 mm Hg) (lit^{2c} 48-50°C, 0.4 mm Hg) 2.29 g (75%) of the product 9 was obtained as a colourless oil.

3-(2, 6, 6-trimethyl-1-cyclohexen-1-yl)-2-propenoic acid (10)

In an 1L erlenmeyer 51.0 g (1.28 mol) NaOH was dissolved in 200 ml water. After cooling the solution with an ice bath 51 g (0.32 mol) bromine was added to the solution. After stirring for 1 h, 13.5 g (70.2 mmol) β -ionone, dissolved in 30 ml of dioxane, was added and the ice bath was subsequently removed. Stirring was continued for 4 h at room temperature, followed by the addition of 300 ml of 10% aqueous sodium bisulfite solution. The solution was extracted with ether (3 x 100 ml). After acidification of the aqueous layer with concentrated HCl the precipitated acid 10 was removed by suction, washed with cold water, and dried in vacuo to yield 12.5 g (92%) 3-(2, 6, 6-trimethyl-1-cyclohexen-1-yl)-2-propenoic acid as a white solid. This product was used in the next reaction step without further purification, but can be crystallized from water/ ethanol yielding the product as white needles, mp 106.5-107.0°C (lit^{2d} mp 105-107°C).

^1H NMR (CDCl_3 , 300 MHz): δ 1.07 (s, 6H), 1.47 (m, 2H), 1.62 (m, 2H), 1.78 (s, 3H), 2.07 (m, 2H), 5.85 (d, J = 16.1 Hz, 1H), 7.56 (d, J = 16.1 Hz, 1H). ^{13}C NMR (CDCl_3): δ 18.78 (t), 21.61 (q), 28.63 (q), 33.58 (t), 33.94 (s), 39.71 (t), 120.59 (d), 135.64 (s), 136.98 (s), 146.57 (d), 172.66 (s).

2, 6, 6-Trimethyl-1-cyclohexene-1-acetaldehyde (9)

To a cooled solution (5°C) of 1.94 g (10.0 mmol) 3-(2, 6, 6-trimethyl-1-cyclohexen-1-yl)-2-propenoic acid¹¹

and 1.10 g (11.0 mmol) triethylamine in 7 ml of dioxane was added in 5 min 3.00 g (11.0 mmol) diphenyl phosphoryl azide¹². After stirring for 1 h at room temperature under N₂, the mixture was diluted with brine (50 ml) and extracted three times with ether (20, 15 and 10 ml). To the concentrated organic extracts was added: 15 ml of dioxane and 10 ml of 0.5 N aqueous hydrogen chloride. The mixture is then refluxed in a preheated oil bath (120°C) under N₂ until the carbon dioxide and nitrogen evolution ceased (12-15 min). The resulting reaction mixture was immediately cooled in an ice bath, diluted with 50 ml brine, extracted with pentane (2 x 25 ml), concentrated and purified by bulb-to-bulb distillation (80°C, 0.5 mm Hg), providing 1.22 g (71%) 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde as a pale yellow liquid. Nearly colorless oil could be obtained by rapid chromatography over a short column of Al₂O₃ (II-III) with CH₂Cl₂/pentane (1/2) as eluents.

¹H NMR (CDCl₃, 300 MHz): δ 0.92 (s, 6H), 1.44 (m, 2H), 1.53 (s, 3H), 1.59 (m, 2H), 1.96 (m, 2H), 3.05 (br.s, 2H), 9.48 (t, J = 2.2 Hz, 1H). ¹³C NMR (CDCl₃): δ 19.22 (t), 20.05 (q), 27.92 (q), 32.75 (t), 39.06 (t), 43.64 (t), 128.40 (s), 132.37 (s), 201.13 (s).

1-[2-(2,6,6-trimethyl-1-cyclohexen-1-yl)-ethenyl]pyrrolidine (12)

In a round bottom flask fitted with a reflux condenser 2.90 g (17.5 mmol) 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde and 1.37 g (19.2 mmol) pyrrolidine were dissolved in 50 ml toluene and heated at 60°C for 1 h. After evaporation of the solvent and bulb-to-bulb distillation of the residue (100°C, 0.15 mm) (lit³ 105°C, 0.7 mm Hg) 3.37 g (88%) of the product was obtained as a colourless oil.

¹H NMR (CDCl₃, 300 MHz): δ 0.98 (s, 6H), 1.43 (m, 2H), 1.55 (m, 2H), 1.72 (s, 3H), 1.85 (m, 4H), 1.96 (m, 2H), 3.03 (m, 4H), 4.52 (d, J = 14.0 Hz, 1H), 6.14 (d, J = 14.0 Hz, 1H). ¹³C NMR (CDCl₃): δ 19.37 (t), 21.93 (q), 24.71 (t), 28.89 (q), 32.98 (t), 34.20 (s), 39.61 (t), 48.98 (t), 95.76 (d), 124.64 (s), 137.06 (s), 138.80 (d).

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