An Approach to the Construction of the Carbon Skeleton of Marine Nor-sesquiterpenes. Total Synthesis of (±)-Dehalo-Napalilactone

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Nesse trabalho descrevemos uma abordagem sintética para a preparação de um esqueleto carbônico que tem dois centros quaternários vizinhos, um dos quais apresenta uma unidade espiro/G67-butyrolactona. Esse arranjo molecular é encontrado em nor-sesquiterpenos isolados de corais marinhos. A estratégia sintética utilizada se baseou no uso de uma reação de adição 1,4 do dimetilcuprato de lítio sobre a 2-metilcicloexenona, seguida da interceptação do enolato intermediário com brometo de alila, para obter a trans-2-álil-2,3-dimetilcicloexanona com moderada diastereoseletividade. Essa última já tem incorporada em sua estrutura um dos centros quaternários do esqueleto. O segundo centro quaternário, que porta a unidade espiro γ-butyrolactona, foi preparado através de uma reação de adição de um reagente organolítico, seguido da separação dos isômeros e de etapas de oxidação. Essa estratégia permitiu obter o esqueleto carbônico dos sesquiterpenos e ao mesmo tempo relatar a síntese total de um derivado nor-sesquiterpênico não natural, em 6 etapas com um rendimento global de 16%, a partir da 2-metilcicloexenona.

We disclose herein a synthetic approach for the preparation of an unusual carbon skeleton, which was found in nor-sesquiterpenes isolated from marine corals. The main structural feature of this skeleton is the presence of two contiguous quaternary centers, one of them bears a spiro γ-butyrolactone moiety. One of the quaternary centers was prepared with moderate stereoselectivity by the conjugate addition of lithium dimethylcuprate to 2-methylcyclohexenone, followed by the trapping of the intermediate enolate with allyl bromide to furnish trans-2-allyl-2,3-dimethylcyclohexan-2-one, as a major diastereoisomer. The preparation of the quaternary centers bearing the spiro γ-butyrolactone moiety was secured by the addition of a suitably functionalized organolithium reagent on trans-2-allyl-2,3-dimethylcyclohexan-2-one, followed by separation of the isomers and two oxidation steps. This strategy has permitted us to report the racemic total synthesis of a non-natural nor-sesquiterpene derivative, in 6 steps and 16% overall yield, from 2-methylcyclohexenone.

Keywords: nor-sesquiterpene, napalilactone, marine natural products, dehalo-napalilactone, pathylactone

Introduction

Chemical studies of the constituents of terrestrial organisms, particularly those of microorganisms and plants have long been carried out, and the development of this field has been remarkable due to the progress made in chemical instrumentation after World War II. Much work on the constituents of animals such as vitamins, hormones and pheromones has been reported1.

However, the search for new compounds from the sea is a relatively recent undertaking. Early studies on the chemistry of marine organisms were the domain of organic chemists, most of whom were concerned with the isolation, chemical characterization and phylogenetic variants of specific substances, for example, types of steroids present in diverse marine animals. A symposium held in 1960 on the biochemistry and pharmacology of compounds derived from marine organisms brought researchers together for the first time and gave cohesion and direction to this field2.

The living environments of marine organisms differ from that of terrestrial organisms, for example, in the seawater the concentration of halides is very high. Due to these differences the constituents in the marine organisms differ considerably from those of the terrestrial organisms.

The presence of halides in seawater has readily allowed...
marine organisms to incorporate bromine, chlorine, and iodine, in that order, into covalent organic structures. Marine organisms contain abundantly halogenated organic compounds, in particular brominated and chlorinated compounds\(^3\).

In 1992, P. J. Scheuer et al.\(^4\) reported the isolation and the structure of a new sesquiterpenoid, Napallactone (1, Figure 1) from the soft coral *Lemnalia africana*. This compound was the first example of a halogenated nor-sesquiterpene to be isolated from a marine organism.

This nor-sesquiterpene is biogenetically derivable from an aristolene carbon skeleton. It presents an unusual structure with two contiguous quaternary centers. One of the quaternary centers bears a spiro \(\gamma\)-butyrolactone unity. Apparently, this halogenated nor-sesquiterpene is part of the coral’s chemical defense system\(^4\).

Recently another nor-sesquiterpene, (pathylactone, 3, Figure 1), having the same structural features, has been isolated by J.-Y. Su et al.\(^5\) from soft coral *Paralemnalia thyrsoides*.

As part of a current research program directed towards the total synthesis of some marine natural products, we disclose herein our results concerning a strategy for the preparation of the carbon skeleton of these nor-sesquiterpenoids. Our interest was focused on the development of a simple and direct methodology, which allowed us to control the relative configuration of the contiguous quaternary centers. Additional modifications in this methodology should permit us to synthesize 1 and 3 (Figure 1), in their racemic forms. In this study we describe the synthesis of (±)-dehalo-napallactone (2), a non-natural nor-sesquiterpenoid derivative.

**Results and Discussion**

From our point of view, the carbon skeleton of the nor-sesquiterpenes 1 and 3 could be prepared from the \(\alpha\)-allyl cyclohexanone 6, through the addition of a suitably functionalized organolithium reagent to furnish the diol 5 (Scheme 1). The preparation of the spiro-\(\gamma\)-butyrolactone moiety could be secured by the oxidative cyclization of
the diol 5, with the correct configuration at C10 (for napalilactone numbering, see Scheme 1). The required ketone 6 could be stereoselectively prepared through a conjugate addition of lithium dimethylcuprate to the double bond of 2-methylcyclohexenone (7), followed by the trapping of the copper enolate intermediate with allyl bromide. The control of the relative stereochemistry of the methyl groups at C4 and C5 (napalilactone numeration) should be secured in this step by this simple sequence (Scheme 1).

The ketone 7 could be easily prepared from 2-methylcyclohexanol using a standard procedure. Depending on the success attained with this strategy, some additional modifications should allow us to synthesize in the future the nor-sesquiterpenes 2 and 3 in their racemic forms.

**Preparation of ketone 6**

The 2-methylcyclohexenone (7) was prepared using a standard procedure in three steps and 73% overall yield from commercial 2-methyl-cyclohexanol. To obtain the carbonyl compound 6 we decided to take advantage of the greater stereoselectivity and generally greater yields of 1,4-addition products obtained using organocopper reagents. Boeckman has described a methodology based on a stereoselective double alkylation of /G61/G2C/G62/unsaturated ketones. The 1,4-addition of lithium dimethylcuprate to 2-methylcyclohexenone, followed by the regioselective alkylation of the copper enolate intermediate with allyl bromide, gave the allyl ketone /6a/b as a diastereoisomeric mixture (GC analysis, cis:trans 20:80) (Scheme 2).

The selectivity obtained in the preparation of ketone 6 can be rationalized by the conformations of the cuprate enolate intermediates A and B (Figure 2). Due to a A12 strain 8,9 conformation B is preferred and the electrophilic attack takes place from the less hindered face of the double bond, thus leading preferentially to the methyl groups in a cis relationship (Figure 2).

The diastereoisomeric mixture was readily separated by column chromatography on silica gel to furnish ketone trans-6b, as a pure isomer in 62% yield. Boeckman reported a diastereoselection ratio of 10:90 (cis:trans). Unfortunately others as well as ourselves were unable to reproduce this result.

The relative stereochemistry of the new stereogenic centers of 6b was confirmed by comparison with the data available in the literature. We have tried to confirm the stereochemical assignments by 1H NMR spectra, by the irradiation of the signals of the methyl groups at C13 and C14. Unfortunately the results were not conclusive, mainly

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Reagents and conditions: a. i) (CH₃)₂CuLi, ether, 0°C; ii) DME, allyl bromide, r.t., 3h, (1:4); iii) chromatographic separation, 75%. b. i) t-BuLi, iodide, -23°C → 0°C, ether, 1h, 68%; ii) ketone 6b, 0°C, 1h, 68% (92% based on recovered starting-material); iii) chromatographic separation c. TMSOTf, CH₂Cl₂, DPEA, -78°C, 6h, quantitative; d) DDQ, CH₂Cl₂/H₂O (18:1), 2.5h then (n-Bu)₄N⁺·F⁻, 1h, 92%; e. TPAP, NMO, 4Å molecular sieves, CH₂Cl₂:CH₃CN 10%, 1h, 80%; f. PdCl₂, Cu(OAc)₂, N,N-dimethylacetamide/water (7:1), O₂, 3 days, r.t., 60%.

Scheme 2. Synthesis of dehalo-napallactone
due to saturation of the signal of the methyl group at C13 when the signal of the C14 methyl group was irradiated and vice-versa.

Preparation of the spiro γ-butyrolactone unity

To prepare the spiro γ-butyrolactone moiety at C10, it was necessary to add a suitably functionalized C3 residue to the ketone 6b. In our view the most direct way to do this was through the 1,2-addition of an organometallic reagent. The C3 residue was readily obtained from 1,3-propanediol by using the methodology recently described by Forsyth and Chen. Treatment of 1,3-propanediol with sodium hydride in THF at 0°C, followed by the addition of p-methoxy-benzyl chloride furnished PMB-ether alcohol intermediate, in 84% yield. The mesylation of the alcohol, followed by substitution with NaI, provided the iodide, in 98% yield for the two steps (see experimental section).

The ketone trans-6b was treated at -23°C with the organolithium compound derived from the iodide (generated by in situ treatment with an ethereal solution of t-butyllithium) to furnish the tertiary alcohol 8, as a mixture of diastereoisomers (ratio 8a/8b 1:1) (Scheme 2).

Unfortunately no stereoselectivity was observed in this step, however the diastereomeric alcohols 8a/8b were easily separated by flash column chromatography.

In order to proceed with our planned synthetic strategy it was necessary to determine the relative stereochemistry of the new stereogenic center. All attempts to do this by 1H NMR (nOe) failed. In fact the results obtained with the nOe experiments were not conclusive. The problem of the relative stereochemistry of the diastereoisomers 8a/8b was solved by the ozonolysis of the separated diastereoisomers at -78°C which after treatment with dimethyl sulfide gave the hemiacetal 12 and the aldehyde 13 (Scheme 4). From our point of view the formation of the hemiacetal 12 from the alcohol 8a is an unambiguous proof that the hydroxyl group and the aldehyde are syn. These results confirmed that the hydroxyl group of alcohol 8a was α oriented and β oriented on alcohol 8b (Scheme 3).

To prepare the spiro-γ-butyrolactone it was necessary to remove the p-methoxybenzyl group. All attempts to cleave this protection group using 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) in the presence of the free tertiary hydroxyl group lead to a mixture, where it was impossible to detect the expected product. To avoid this problem the tertiary alcohol 8a was first transformed to the trimethylsilyl ether 9 (Scheme 2). Then the silyl ether 9 was treated with DDQ in dichloromethane/water, followed by the addition of tetrabutylammonium fluoride (n-Bu4NF) to remove the silyl group. This simple protocol provided the diol 5 in 92% yield for the two steps (Scheme 2).

The diol 5 was readily transformed into the spiro-γ-
butyrolactone 10 by treatment with tetraisopropylammoniumperbutylate (TPAP) in the presence of molecular sieves (4Å) and morpholine N-oxide (NMO), in accordance with the methodology described by Mehta and Karra. Under these conditions the primary hydroxyl group was oxidized to an aldehyde which was transformed in situ into a hemiacetal intermediate, which was oxidized to the lactone 10 (Scheme 2).

At this stage we had incorporated almost all the functionality of the nor-sesquiterpene structure with the suitable relative configuration. To complete our reaction sequence the product 10 was submitted to a modified Wacker reaction. The lactone 10 was treated with PdCl2 and CuI in a mixture of N,N-dimethylacetamide and H2O (7:1) to furnish the (±)-dehalo-napalilactone (2), as a white solid (Scheme 2).

**Experimental**

**General**

The 1H and 13C NMR spectra were recorded on a Varian GEMINI BB-300 at 300MHz and 75.1 MHz respectively. The 1H spectra were also recorded in an AW-80 Bruker at 80MHz and Inova 500MHz. The mass spectra were recorded using a CG/MS HP model 5988A and an Autospec-Micromass 80MHz and Inova 500MHz. The mass spectra were recorded in an AW-80 Bruker at 90MHz and Inova 500MHz.

**Synthesis of (±)-2-allyl-2,3-dimethylcyclohexan-1-one (6a/6b)**

A suspension of CuI (7.79 g, 41.0 mmol) in anhydrous ether (90 cm3) was added an ethereal solution of methylthiolium (65 cm3, 82.0 mmol, ca. 1.25 mol dm-3), at 0°C, under an inert atmosphere of N2. After 15 min at 0°C, a solution of 7 (3.0 g, 27.27 mmol) in anhydrous ether (30 cm3) was added to the ethereal solution of lithium dimethylcuprate. After 60 min, at 0°C the solvent was removed under reduced pressure (CAUTION: Avoid drying the reaction media completely as it is well known in the literature that some dry RCu compounds can explode). To the resulting yellow wet solid was added DME (65 cm3), under a N2 atmosphere giving rise to a greenish black solution, to which allyl bromide (19.0 cm3, 218 mmol) was added, at 0°C. The final solution was stirred for 15 min. After that, the reaction was quenched with a saturated solution of NaHCO3 (200 cm3), followed by the addition of a 10% solution of NH4OH (45 cm3). The blue aqueous phase was extracted with pentane (3 x 200 cm3). The combined organic layers were washed with a 10% solution of NaHCO3 (50 cm3) and distilled water (100 cm3).

**Ketone cis-6a:** IR νmax/cm-1 3073, 2960, 2924, 2871, 1716, 1456, 1385, 1319, 1141, 1034, 909, 808 (film); 1H NMR (500 MHz, CDCl3) δ 5.61-5.54 (m, 1H), 5.07-5.0 (m, 2H), 2.49 (dd, J 14.0 and 7.6 Hz, 1H), 2.42-2.38 (m, 1H), 2.34-2.30 (m, 1H), 2.11 (1H, dd, J 14.0 and 7.0 Hz), 2.03-1.97 (m, 1H), 1.75-1.64 (m, 4H), 1.09 (s, 3H), 0.98 (d, J 6.6 Hz, 3H).

**Ketone trans-6b:** IR νmax/cm-1 3073, 2960, 2924, 2871, 1716, 1456, 1385, 1319, 1141, 1034, 909, 808 (film); 1H NMR (CDCl3) δ 5.80-5.66 (m, 1H), 5.07-5.00 (m, 2H), 2.52 (dd, J 14.0 and 8.4 Hz, 1H), 2.47-2.28 (m, 2H), 2.17 (dd, J 14.0 and 8.4 Hz), 2.0-1.87 (m, 2H), 1.85-1.75 (m, 1H), 1.74-1.65 (m, 1H), 1.64-1.50 (m, 1H), 1.0 (s, 3H), 0.91 (d, J 7.0 Hz, 3H); 13C NMR (75.4 MHz, CDCl3) δ 216.2, 135.4, 117.6, 52.3, 40.8, 38.5, 38.4, 29.1, 24.3, 18.9, 15.2.

**Synthesis of 1-[(4-methoxybenzyl)oxy]-3-propyl iodide (11)**

To a suspension of NaH (1.6 g, 39.6 mmol, 60% in mineral oil, washed with dry hexane before use) in dry THF (220 cm3), at 0°C, under argon, was added 1,3-propanediol (1.3 g, 33 mmol). The resulting mixture was warmed to room temperature and stirred for 1h. After this time, the mixture was cooled to 0°C and to the cooled suspension was added tetraethylammonium iodide (2.44 g, 6.61 mmol) and p-methoxybenzylchloride (PMBCl, 5.4 cm3, 39.6 mmol). The reaction mixture was warmed again to room temperature and stirred for 24h. The reaction mixture was subsequently hydrolysed by the addition of a saturated solution of NH4Cl (100 cm3) and extracted with ethyl ether (2 x 250 cm3). The organic phase was washed with a saturated solution of NH4Cl (75 cm3), distilled water (2 x 75 cm3), brine (2 x 75 cm3) and dried over anhydrous Na2SO4. After the evaporation of the solvent under reduced pressure, the residue was purified by column chromatography to furnish 1-[(4-methoxybenzyl)oxy]-3-propanol.
(5.43 g, 84%), as a colorless oil.

IR ν<sub>max </sub>/cm<sup>-1</sup> 3412, 3007, 2948, 2871, 2062, 1997, 1896, 1622, 1468, 1373, 1313, 1260, 1177, 1087, 1034, 832 (film); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.25 (d, J 8.8 Hz, 2H), 6.87 (d, J 8.8 Hz, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 3.75 (t, J 6.0 Hz, 2H), 3.62 (t, J 6.0 Hz), 2.65-2.25 (bs, 1H), exchangeable with D<sub>2</sub>O, 1.84 (quint, J 6.0 Hz, 2H); <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): δ 159.2, 130.1, 129.2, 113.8, 72.8, 68.9, 61.7, 55.2, 32.0.

To a solution of alcohol obtained above (3.0g, 13.3 mmol) in dry dichloromethane (105 cm<sup>3</sup>) was slowly added, at 0°C, triethylamine (2.3 cm<sup>3</sup>, 16.8 mmol) and mesyl chloride (1.55 cm<sup>3</sup>, 20 mmol). To the resulting mixture was added a solution of 4-dimethylaminopyridine (DMAP) in dry dichloromethane (105 cm<sup>3</sup>) and the solvent evaporated under reduced pressure. The mixture of diastereomeric alcohols (CG 50:50 ratio) was easily separated by flash column chromatography (silica gel 230-400 mesh, eluting with hexane-ethyl acetate 99:1 and 95:5 v/v) to furnish the alcohol 8a (0.24g, 34% or 46% based on the recovered starting material) and the alcohol 8b (0.24 g, 34% or 46% based on the recovered starting material).

Alcohol 8a: IR ν<sub>max </sub>/cm<sup>-1</sup> 3459, 3079, 2936, 2871, 1616, 1515, 1474, 1373, 1313, 1248, 1183, 1099, 1046, 915, 826, 749 (film); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.26 (d, J 8.8 Hz, 2H), 6.88 (d, J 8.8 Hz, 2H), 6.10 (m, 1H), 5.07 (m, 1H), 5.02 (m, 1H), 4.44 (s, 2H), 3.80 (s, 3H), 3.49-3.45 (m, 2H), 2.24-2.11 (m, 2H), 2.01-1.92 (m, 1H), 1.81-1.67 (m, 2H), 1.64-1.43 (m, 2H), 1.39-1.21 (m, 2H), 1.0 (s, 3H), 0.84 (d, J 6.6 Hz, 3H); <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 159.1, 138.3, 130.7, 129.1, 116.5, 113.7, 77.3, 72.3, 70.7, 55.2, 45.1, 41.5, 37.5, 30.8, 30.3, 30.1, 23.3, 22.0, 16.6, 13.0; MS (70eV , m/z): 346 (M+, 3%), 287 (2%), 207 (6%), 121 (100%), 77 (7%); HRMS (M+) Calc. for C<sub>22</sub>H<sub>34</sub>O<sub>3</sub> 346.25080; Found: 346.25072.

Alcohol 8b: IR ν<sub>max </sub>/cm<sup>-1</sup> 3459, 3079, 2924, 2936, 2859, 1616, 1527, 1468, 1367, 1307, 1248, 1183, 1111, 1046, 927, 826 (film); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.26 (d, J 8.8 Hz, 2H), 6.87 (d, J 8.8 Hz, 2H), 6.14 (m, 1H), 5.08 (m, 1H), 5.01 (m, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.50-3.40 (m, 2H), 2.37 (dd, J 10.0 and 9.5 Hz, 1H), 2.28-2.13 (m, 2H), 1.95 (brs, exchangeable with D<sub>2</sub>O, 1H), 1.79-1.22 (m, 10H), 0.85 (d, J 6.6 Hz, 3H), 0.78 (s, 3H); <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 159.0, 138.8, 130.6, 129.2, 116.2, 113.7, 77.4, 72.3, 70.8, 55.2, 44.7, 39.9, 33.3, 31.8, 31.5, 30.2, 23.4, 21.1, 17.3, 16.1; MS (70eV, m/z): 346 (M+, 3%), 287 (2%), 207 (6%), 121 (100%), 77 (7%); HRMS (M+) Calc. for C<sub>22</sub>H<sub>34</sub>O<sub>3</sub> 346.25080; Found: 346.25072.

Synthesis of (±)-2-allyl-1-[3-(4-methoxybenzyloxy)propyl]-2,3-dimethylcyclohexan-1-ol (8a/8b)

To a stirred solution of the iodide 11 (0.91 g, 3.0 mmol) in anhydrous ether (20 cm<sup>3</sup>) was added t-butylithium (4.48 cm<sup>3</sup>, 3.0 mmol) at -78°C, under N<sub>2</sub> atmosphere. The resulting solution was stirred for 20 min at -78°C and allowed to warm to 0°C, before a solution of the ketone 6b (0.33g, 2.0 mmol) in anhydrous ether (20 cm<sup>3</sup>) was slowly added (via canula). The final solution was stirred for 60 min at 0°C. The reaction medium was quenched with a saturated solution of NH<sub>4</sub>Cl (13 cm<sup>3</sup>) and extracted with ether (2 x 65 cm<sup>3</sup>). The combined organic layers were washed with a saturated solution of NH<sub>4</sub>Cl (40 cm<sup>3</sup>), distilled water (2 x 40 cm<sup>3</sup>) and finally brine (2 x 40 cm<sup>3</sup>). The combined aqueous layers were extracted twice with ether (65 cm<sup>3</sup>). The combined organic layers were dried over MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. The mixture of diastereoisomeric alcohols (CG 50:50 ratio) was easily separated by flash column chromatography (silica gel 230-400 mesh, eluting with hexane-ethyl acetate 99:1 and 95:5 v/v) to furnish the alcohol 8a (0.24g, 34% or 46% based on the recovered starting material) and the alcohol 8b (0.24 g, 34% or 46% based on the recovered starting material).

Alcohol 8a: IR ν<sub>max </sub>/cm<sup>-1</sup> 3001, 2936, 2894, 2865, 1616, 1518, 1474, 1373, 1313, 1248, 1183, 1099, 1046, 915, 826, 749 (film); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.8 Hz, 2H), 6.87 (d, J 8.8 Hz, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.51 (t, J 6.0 Hz, 2H), 3.29 (t, J 6.7 Hz, 2H), 2.07 (quint, J 6.0 Hz, 2H); <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 159.2, 130.3, 129.3, 113.8, 72.7, 69.3, 55.2, 33.5, 3.5.

Synthesis of (±)-2-allyl-1-[3-(4-methoxybenzyloxy)propyl]-2,3-dimethylcyclohexan-1-trimethylsilyloxyether (9)

To a stirred mixture of alcohol 8a (0.06g, 0.173 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (0.6 cm<sup>3</sup>) and DIPEA (0.3 cm<sup>3</sup>, 1.73 mmol) at -78°C was slowly added TMSOTf (0.30 cm<sup>3</sup>, 0.173 mmol). After 4h the cooling bath was removed and...
the reaction medium was warmed to room temperature, stirring was maintained for another 4h. After that, methanol (6 cm³) was added and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel 230-400 mesh, eluting with hexane-ethyl acetate 99:1) to furnish 9 (0.072 g, quantitative yield) as a colorless oil.

IR ν [cm⁻¹] 3073, 2960, 2859, 1616, 1527, 1468, 1064, 1040, 838 (film); ¹H NMR (300 MHz, CDCl₃) δ 7.24 (d, J 8.8 Hz, 2H), 6.84 (d, J 8.8 Hz, 2H), 6.07-5.93 (m, 1H), 4.87-4.78 (m, 2H), 4.41 (s, 2H), 3.77 (s, 3H), 3.48-3.34 (m, 2H), 2.12-2.01 (m, 2H), 1.84-1.78 (m, 1H), 1.62-1.45 (m, 2H), 1.36-1.13 (m, 2H), 0.81 (s, 3H), 0.8 (d, J 6.6 Hz, 3H), 0.93 (d, J 6.6 Hz, 3H); ¹³C NMR (75.4 MHz, CDCl₃) δ 159.0, 138.9, 130.8, 129.2, 113.5, 113.7, 81.7, 72.3, 70.9, 55.2, 45.3, 41.5, 37.8, 32.2, 30.6, 30.5, 24.0, 22.7, 17.1, 14.1, 3.1.

Synthesis of (±)-2-allyl-1-(3-hydroxypropyl)-2,3-dimethylcyclohexan-1-ol (5)

To a solution of PMB-ether (0.071 g, 0.17 mmol) in a mixture of CH₂Cl₂ (4 cm³) and distilled water (0.22 cm³) was added powder molecular sieves (4Å, 0.066 g), morpholine N-oxide (NMO, 0.0312 g) and tetrapropylammonium perruthenate (TPAP, 0.004 g 0.17 mmol). The resulting solution was stirred for 4h. After that the crude reaction was filtered through a silica gel (230-400 mesh) chromatographic column (eluting with hexane:ethyl acetate 80:20) to furnish (±)-10 (0.0235, 80%), as a colorless oil.

IR ν [cm⁻¹] 3079, 2936, 2871, 1771(CO), 1640, 1462, 1218, 1171, 1004, 927 (film); ¹H NMR (300 MHz, CDCl₃) δ 6.0-5.87 (m, 1H), 5.02-4.99 (m, 1H), 4.96-4.94 (m, 1H), 2.63-2.43 (m, 2H), 2.39-2.26 (m, 2H), 2.08 (dd, J 14.8 and 8.8 Hz, 1H), 1.96-1.87 (m, 2H), 1.55-1.19 (m, 6H), 1.06 (s, 3H), 0.93 (d, J 6.6 Hz, 3H); ¹³C NMR (75.4 MHz, CDCl₃) δ 177.0, 136.2, 115.3, 92.0, 43.3, 42.1, 36.9, 33.9, 29.7, 29.0, 28.8, 26.2, 15.8, 14.7; MS (70eV, m/z): 222 (M+, 100%), 207 (6%), 151 (20%), 122 (40%), 107 (43%), 69 (26%); HRMS (M+) Calc. for C₄₄H₇₂O₂ 222.16198. Found 222.16201.

Synthesis of (±)-dehalo-napalilactone (2)

A suspension of the lactone 10 (0.012 g, 0.054 mmol), PdCl₂ (0.001 g, 0.005 mmol) and Cu(OAc)₂.H₂O (0.003 g, 0.011 mmol) in N,N-dimethylacetamide (0.079 cm³ or 79 μL) and distilled water (0.013 cm³ or 13 μL) was stirred at room temperature for 3 days under an O₂ atmosphere. After which time HCl (3 mol dm⁻³ solution, 0.180 cm³) was added to the solution and the reaction mixture was extracted with ether (5 x 3 cm³). The organic layer was washed with a saturated solution of NaHCO₃ (10 cm³), brine (10 cm³) and dried over anhydrous MgSO₄. After the evaporation of the solvent under reduced pressure the residue was purified by flash chromatography (eluting with hexane:ethyl acetate 70:30) to furnish the diol 5 (0.038 g, quantitative yield), as a colorless oil.

IR(ν [cm⁻¹]) 3000-3500, 2960, 2859, 1616, 1527, 1468; ¹H NMR (300 MHz, CDCl₃) δ 6.17-6.05 (m, 1H), 5.15-5.06 (m, 2H), 3.48 (t, J 6.6 Hz, 2H), 2.45 (brs, 1H, exchangeable with D₂O), 2.28-2.14 (m, 2H), 2.05-1.96 (m, 1H), 1.63-1.5 (m, 2H), 1.41-1.33 (m, 2H), 1.31-1.22 (m, 2H), 1.01 (s, 3H), 0.86 (d, J 6.6 Hz, 3H); ¹³C NMR (75.4 MHz, CDCl₃) δ 138.2, 116.8, 77.7, 61.7, 45.1, 41.4, 37.6, 31.5, 30.8, 26.3, 22.0, 19.2, 16.6, 13.0; MS (70eV, m/z): 226 (M+, 6%), 167 (50%), 124 (45%), 109 (25%), 97 (100%), 83 (30%), 69 (325); HRMS (M+) Calc. for C₁₄H₂₂O₂ 226.19328. Found 226.19331.

Synthesis of (±)-6-allyl-6,7-dimethyl-1-oxaspiro[4.5]decan-2-one (10)

To a solution of diol 5 (0.03 g, 0.133 mmol) in a mixture of CH₂Cl₂:CH₃CN (9:1, 0.33 cm³) were added powder molecular sieves (4Å, 0.066 g), morpholine N-oxide (NMO, 0.0312 g) and tetrapropylammonium perruthenate (TPAP, 0.004 g 0.11 mmol). The resulting solution was stirred for 1h. After that the crude reaction was filtered through a silica gel (230-400 mesh) chromatographic column (eluting with hexane:ethyl acetate 80:20) to furnish (±)-10 (0.0235, 80%), as a colorless oil.

IR ν [cm⁻¹] 3079, 2936, 2871, 1771(CO), 1640, 1462, 1218, 1171, 1004, 927 (film); ¹H NMR (300 MHz, CDCl₃) δ 6.0-5.87 (m, 1H), 5.02-4.99 (m, 1H), 4.96-4.94 (m, 1H), 2.63-2.43 (m, 2H), 2.39-2.26 (m, 2H), 2.08 (dd, J 14.8 and 8.8 Hz, 1H), 1.96-1.87 (m, 2H), 1.55-1.19 (m, 6H), 1.06 (s, 3H), 0.93 (d, J 6.6 Hz, 3H); ¹³C NMR (75.4 MHz, CDCl₃) δ 177.0, 136.2, 115.3, 92.0, 43.3, 42.1, 36.9, 33.9, 29.7, 29.0, 28.8, 26.2, 15.8, 14.7; MS (70eV, m/z): 222 (M+, 100%), 207 (6%), 151 (20%), 122 (40%), 107 (43%), 69 (26%); HRMS (M+) Calc. for C₁₄H₂₂O₂ 222.16198. Found 222.16201.

Conclusion

In conclusion, this simple and direct strategy has
permitted us to describe the first racemic total synthesis of dehalo-napalilactone (2), a non-natural sesquiterpene. Dehalo-napalilactone (2) was prepared in 6 steps from methycyclohexene with an overall yield of 16%. Additional modifications to this strategy are ongoing in our laboratory, our objective being the total synthesis of (±)-napalilactone (1) and (±)-pathylactone (3).

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References


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