Chemical Transformation of Abietic Acid to New Chiral Derivatives

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Neste trabalho descrevemos as reações de transformações químicas do anel C do ácido abiético (1\textit{a}) com o objetivo de gerar novos síntons quirais. A partir do intermediário cetó-aldeído 9, obtido através da reação de ozonólise do abietato de metila (1\textit{b}), foram sintetizados derivados bicíclicos tais como 14, 15 e 16 e um novo diterpeno tetracíclico 4. Foram também sintetizados, a partir 17, novos derivados contendo esqueleto abeo-abiétano[6,6,5] tais como 19 e 20.

Chemical transformations of the C-ring abietic acid (1\textit{a}) for the preparation of some new chiral synthons are described. From the intermediate keto-aldehyde 9, readily available from 1\textit{b} through the ozonide 2, the new tetracyclic diterpene 4 was synthesized. Additionally, from 13 and 17, previously prepared from 2, the bicyclic compounds 14, 15 and 16 and the derivatives containing the abeo-abiétane[6,6,5] framework 19 and 20 were also synthesized.

Keywords: abietic acid, ozonization, chiral synthon, abeo-abiétane derivatives

Introduction

Abietic acid (Figure 1, 1\textit{a}) is a diterpene readily available from an oleoresin produced by Pinus elliottii\textsuperscript{1} that shows activity as a chemical defense against insect and pathogenic fungi and bacteria.\textsuperscript{2} This acid has been used widely as an enantiomerically pure starting material in organic synthesis.\textsuperscript{3} Examples are the syntheses of Ambrox\textsuperscript{4}, warburganal\textsuperscript{5} and some other sesquiterpenes.\textsuperscript{6} In order to evaluate the biological activities of the compounds obtained by modifying the framework of methyl ester 1\textit{b}, we first synthesized the stable ozonide 2 that showed activity against some lines of non-small lung cell, melanoma and breast cancers.\textsuperscript{6} We have also shown that some Diels-Alder adducts of 1\textit{b} presented activities against Staphylococcus aureus, Bacillus subtilis and Micrococcus luteus.\textsuperscript{7} Starting with 2 we recently completed the synthesis of 3,\textsuperscript{8} an analogue of a new class of compound named oidiolactone.\textsuperscript{9} In this paper we describe the transformation of 9 into the new tetracyclic derivative 4 and into its known diastereoisomer 5,\textsuperscript{9} the transformation of 13 into the bicyclic compounds 14, 15 and 16 and also transformation of 17 into the new

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Results and Discussion

To explore a different reactivity of the double bonds in the B and C-rings of 1\textit{b}, preliminary semi-empirical calculations (AM1 and PM3) were carried out using the SPARTAN\textsuperscript{10} and Hyperchem\textsuperscript{11} programs.\textsuperscript{11} The first analysis made was the Mulliken charges (Figure 2 - A and B) which showed the C-ring to have a small, but higher, coefficient
than the B-ring. On the other hand, HOMO coefficient calculations showed a slightly higher coefficient for C-7 than C-13 (Figure 2 - C).

These results led us to conclude that an electrophilic attack can occur either on the double bond at C-7 or at C-13, and that the regioselectivity would depend on the reaction conditions and reactivity of the reagents. The literature gives examples where treatment of 1b with OsO₄ or an epoxidation reaction with mCPBA occurred preferentially on the C-ring. The oxidation of 1b with I₂/KHCO₃ at 50 °C (THF:H₂O; 47:1) also occurred on the C-ring and furnished the β-epoxide 6. However, when the reaction was carried out at 30 °C, the C-7 oxo-derivative 7 (Figure 3) was obtained as the main product, showing that the reaction had occurred on the B-ring.

In a previous study we reported that the ozonolysis reaction of 1b in CH₂Cl₂ furnished compound 2, showing that the reaction took place at the C-7 and C-13 double bonds. Carrying out the reaction using MeOH-CH₂Cl₂ (1:1) as solvent, we obtained compound 8 in 28% yield (Figure 3), in addition to a highly polar polymerized material. The formation of compound 8 showed that, under this condition, the electrophilic attack occurred at C-7 and C-13 double bond of 1b.

Compound 8 was characterized by ¹H NMR spectral analysis where the signal at δ 4.08 (s, 1H) was assigned to H-14 and the signals at δ 3.39, 3.43 and 3.64 were attributed to the methoxy groups of the acetal moiety and the methyl ester, respectively. The presence of an epoxy group at C-7 was observed in the ¹H NMR spectrum, through the signal of H-7 at δ 3.21, and was confirmed by ¹³C NMR spectrum which showed signals of C-7 and C-8 at δ 54.6 (CH) and at δ 59.8 (C), respectively. The chemical shifts at δ 56.2 and at δ 57.1 confirmed the presence of the two methoxy groups of the acetol moiety at C-14 and the carbomethoxy group was observed at δ 52.0. Two carbonyl carbons, one at δ 178.5 assigned to the ester (C-18), and another at δ 214.6, assigned to the ketone (C-13) were also observed. All other signals were in agreement with those observed for abietane models.

In an attempt to cleave the side chain of the bicyclic intermediate 9, we submitted it to a Baeyer-Villiger reaction induced by mCPBA. Two compounds were isolated from the crude reaction product and were spectroscopically characterized as the tetracyclic compounds 4 (50%) and 5 (33%), instead of the expected product 10 (Scheme 1).

The ¹H NMR spectrum of 4 showed a triplet at δ 3.93 (J 2.8 Hz) assigned to H-7, two multiplets at δ 1.79 and δ 1.88 assigned to H-12 and two singlets at δ 1.10 and δ 1.22 assigned, respectively, to the methyl groups at C-20 and C-19. The ¹³C NMR spectrum showed chemical shifts at δ 16.1 and at δ 16.2, which were assigned to the methyl groups at C-20 and C-19. The ¹³C NMR spectrum showed chemical shifts at δ 114.1 and at δ 114.1, which were assigned to the methyl groups at C-16 and C-17 and the signal at δ 177.2 was assigned to the carbonyl carbon of the lactone (C-14) and the presence of a carbonyl group was confirmed through the IR absorption at 1768 cm⁻¹. All spectroscopic data were in good agreement with those reported for the model ambraketal analogues 11 and 12, previously synthesized by Scheidegger et al. (Figure 4) as well as for abietane model compounds. Compound 5 was also characterized by spectroscopic data analysis and through comparison with those reported previously by Haslinger (Figure 4).

In view of these results we decided to study an alternative sequence, starting with 13 to cleave its side chain. Our first choice was to analyze the preparation of intermediate 15 (Scheme 2).

The reduction of 13 with NaBH₄/MeOH furnished, as expected, an inseparable mixture of epimeric alcohols 14.
in 80% yield. The $^1$H NMR spectrum of this mixture showed a multiplet at $\delta$ 3.34, which was assigned to H-13, and the $^{13}$C NMR spectrum the signal at $\delta$ 76.6 was also attributed to C-13. Following the sequence, the dehydration reaction of 14 was carried out using POCl$_3$ where a mixture of olefins 15/16 (88:12) was obtained in 33% yield. The best result was obtained when alcohol 14 was reacted with MsCl, followed by treatment with DBU-Bz$^+$ to furnish a mixture of 15/16 (88:12) in 54% yield.

![Figure 4. Structures of abietane derivatives 4 and 5 and ambraketal derivatives 11 and 12.](image)

Scheme 2. Syntheses of 15 and 16 from 13.

Compound 15 was characterized by $^1$H NMR spectral analysis where a chemical shift of H-13 as a broad triplet at $\delta$ 5.04 (J 7.2 Hz) and methyl groups of H-16 and H-17 attached to sp$^2$ carbons at $\delta$ 1.60 and at $\delta$ 1.69 were observed. The $^{13}$C NMR spectrum showed the signal of C-15 at $\delta$ 132.2 (C) and the signal of C-13 at $\delta$ 125.2 (CH) confirming the presence of the double bond. For compound 16, the chemical shift of H-12 was observed at $\delta$ 5.25 (ddd, J 15.8; 7.2 and 4.0 Hz) and the chemical shift at $\delta$ 5.41 (dd, J 15.8 and 6.0 Hz) was assigned to H-13. The chemical shift of H-15 appeared at $\delta$ 2.22 as a doublet and H-16 and H-17 appeared as a doublet at $\delta$ 0.94. The presence of the double bond was also confirmed through $^{13}$C NMR spectral analysis where the chemical shift of C-12 was observed at $\delta$ 123.7 (CH) and the chemical shift of C-13 was observed at $\delta$ 139.8.

Since 13 is a highly oxygenated compound containing a very reactive oxirane ring and knowing that the transformation of the epoxide to the corresponding olefin is feasible, compound 13 was submitted to reaction with thiourea oxide$^{18}$ and PPh$_3$/I$_2$. In both cases only the starting material was recovered and attempts to open the epoxide to the corresponding diol using different conditions, such as 85% KOH/DMSO,$^{20}$ H$_2$SO$_4$/acetone$^{21}$ or KOH/H$_2$O also failed. Further investigations on the bicyclic system to obtain potentially biologically active compounds such as anticancer, bactericidal and fungicidal compounds are now underway.

In order to obtain a more advanced chiral intermediate than the tricyclic compound 17, which was previously prepared in a reasonable yield (45%, 2 steps)$^{6}$ from 2, an oxidation reaction of the hydroxyl group at C-17 was considered. Unfortunately, the oxidation reaction using different reagents, such as calcium hypochloride,$^{22}$ Moffatt oxidation$^{23}$ and Jones reagent,$^{21}$ led only to an intractable mixture of products or recovery of the starting material.

![Scheme 3. Oxidation reaction of 17.](image)

Surprisingly, treatment of 17 with PCC$^{24}$ led to the triol 19 in 30% yield instead of to the expected oxidized product 18. This triol was characterized through $^1$H NMR spectral analysis, where a signal at $\delta$ 4.35 (dd, J 12.0 Hz and J 6.0 Hz) assigned for H-7, clearly deshielded when compared with H-7 of 17 (s, $\delta$ 3.27), was observed, consistent with equatorial orientation of the hydroxyl group. All other signals, including H-12 at $\delta$ 3.15 (ddd, J 13.5; 7.5 and 5.2 Hz), were in agreement with the structure depicted as 19. The HRMS data (M$^+$ at $m/z$ 382.23553) also confirmed the molecular formula C$_{23}$H$_{34}$O$_6$. The $^{13}$C NMR spectrum showed the chemical shifts of C-7 and C-8 at $\delta$ 70.0 (CH) and 81.0 (C), respectively, and was consistent with the structure proposed as 19. The IR spectrum also showed three absorptions of hydroxyl group at 3546, 3515 and 3549 cm$^{-1}$. Conversion of the epoxide to the diol in high selectivity, using chromium complexes like [Cr(N-tBu)Cl$_3$(dme)] or [V(Ntol)Cl$_3$] (dme = 1,2-dimethoxyethane, tol = p-tolyl) is known in the literature and,
according to Leung et al., formation of a five-membered ring chelate seems to be more favorable than the six-membered ring. Probably the chelation of the chromium ion with the oxygen of the epoxide and the hydroxyl group at C-12 from the α face, led to the attack of water from the β face (at C-7), to furnish the trans diol, as shown in Scheme 4.

Scheme 4. Proposal of the mechanism for the synthesis of 19.

Due to the difficulties found in oxidizing compound 17, a Baeyer-Villiger reaction followed by oxidation and decarboxylation, in order to obtain 21, was considered. Following this sequence, treatment of 17 with mCPBA furnished 20 in 80% yield (Scheme 5).

Scheme 5. Baeyer-Villiger oxidation of 17.

The 1H NMR spectrum of 20 showed the chemical shift of methyl groups at 1.26 (d, J 6.2 Hz, 3H, H-16) and 1.28 (d, J 6.2 Hz, 3H, H-17), slightly deshielded in comparison with those of 17 (δ 1.13; d, J 6.2 Hz), as well as H-15 which now appeared at δ 5.08 (sept, J 8 Hz). The 13C NMR spectrum of 20 showed the chemical shift of methyl groups at δ 21.8 (C-16) and δ 21.9 (C-17) and a carbinolic carbon C-15 at δ 68.2. The IR absorption at 1725 cm⁻¹ and the 13C NMR chemical shift at δ 173.4 (C-13) confirm the presence of a carbonyl ester and the success of Baeyer-Villiger oxidation reaction. Unfortunately, the oxidation reaction of the secondary alcohol of 20 using PCC or Jones reagent led only to recovery of the starting material.

None of the synthesized compounds presented significant activity against Artemia salina and any activities against S. aureus, B. subtilis and M. luteus. Further work is in progress in order to obtain a more elaborated tricyclic chiral synthon for the synthesis of drimane sesquiterpenes and biologically active compounds.

Experimental

NMR spectra were recorded on a Gemini 300P–Varian Instruments and Bruker AC (1H NMR at 300 MHz and 13C NMR at 75 MHz) or on an INOVA 500–Varian Instruments (1H NMR at 500 MHz and 13C NMR at 125 MHz), in CDCl₃ as solvent with TMS as internal standard. IR spectra were measured on a Perkin Elmer 1600 or on a BOMEM MB-100 FTIR. Optical rotation was measured on a Carl Zeiss photoelectric polarimeter. High-resolution mass spectra (HRMS) were recorded with a VG 7070E spectrometer. For the HOMO/LUMO and Mulliken charge calculations, the programs PC SPARTAN® plus (version 1.5) and Hyperchem 6.03 professional® were used. Column chromatography was performed by using Merck silica gel 60 (70-230 mesh) and TLC plates were performed using Merck 60F₂₅₄ silica gel on glass-supported plates.

Synthesis of 8 from 1b

A stream of ozone was passed through a solution of 1b (238.0 mg, 0.78 mmol) in anhydrous CH₂Cl₂/MeOH (1:1) (26.0 mL) at -78 °C until a blue color persisted. Excess ozone was removed by passing nitrogen through the solution and the reaction mixture was treated with PPh₃ (26.0 mL) at -78 °C until a blue color persisted. Excess ozone was removed by passing nitrogen through the solution and the reaction mixture was treated with PPh₃ (26.0 mL) at -78 °C until a blue color persisted.

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**Syntheses of 4 and 5 from 9**

To a solution of 9 (50.0 mg, 0.27 mmol) in anhydrous \( \text{CH}_2\text{Cl}_2 \) (5.0 mL) was added 99% mCPBA (48.0 mg, 0.54 mmol) and NaHCO$_3$ (12.0 mg, 0.27 mmol). The reaction mixture was kept in the dark with stirring at room temperature for 15 days. The mixture was filtered and the organic layer was washed with saturated NaHCO$_3$ solution. The organic layer was dried over anhydrous MgSO$_4$ and the solvent was evaporated in a rotary evaporator. The residue was chromatographed on silica gel (n-hexane-EtOAc, 85:15) to furnish two products. Compound 4 (25.5 mg, 50%) was obtained as a colorless oil; [α]$^20$$^\text{D}$ -11.5 (c 1.5, CHCl$_3$); IR (film) \( \nu_{\text{max}} \) /cm$^{-1}$: 3511, 2975, 1768, 1725, 1389, 1250, 1162, 1072, 737; $^1$H NMR (300 MHz) \( \delta \): 0.94 (m, 1H, H-1), 1.00 (d, J 7.70 Hz, 3H, H-16), 1.03 (d, J 7.70 Hz, 3H, H-17), 1.10 (s, 3H, H-20), 1.22 (s, 3H, H-19), 1.32 (dd, J 14.4, 3.0, 2.2 Hz, 1H, H-6), 1.58 (m, 1H, H-3), 1.62 (m, 2H, H-2), 1.76 (m, 1H, H-6'), 1.78 (m, 1H, H-9), 1.79 (m, 1H, H-12), 1.80 (m, 1H, H-1'), 1.82 (m, 1H, H-3'), 1.88 (m, 1H, H-11), 2.04 (sept, J 6.8 Hz, 1H, H-5, -OH), 3.20 (t, J 6.8 Hz, 1H, H-11'), 1.66 (m, 1H, H-6), 1.78 (m, 1H, H-3'), 1.82 (m, 1H, H-11), 1.38 (m, 1H, H-9), 1.49 (m, 1H, H-14), 1.54 (m, 2H, H-2), 1.57 (m, 1H, H-3), 1.61 (m, 2H, H-12), 1.64 (m, 1H, H-11'), 1.66 (m, 2H, H-6), 1.78 (m, 1H, H-3'), 1.82 (m, 1H, H-1'), 1.86 (m, 2H, H-5, -OH), 3.20 (t, J 2.6 Hz, 1H, H-7), 3.34 (m, 1H, H-13), 3.66 (s, 3H, H-21), 3.74 (s, 3H, H-22); $^{13}$C NMR (75 MHz) \( \delta \): 14.7 and 14.8 (C-20), 17.0 (C-19), 17.2 and 17.4 (C-16), 18.1 (C-2), 18.6 (C-17), 20.4 and 20.7 (C-11), 23.7 (C-6), 33.2 and 32.8 (C-12), 33.6 and 33.7 (C-15), 34.6 and 34.7 (C-10), 36.8 (C-3), 37.6 (C-1), 41.2 (C-5), 46.5 (C-4), 52.1 (C-21), 52.3 (C-22), 53.8 (C-9), 57.2 (C-7), 58.9 (C-8), 76.6 (C-13), 170.7 and 170.9 (C-14), 178.4 (C-18); HRMS: Calcd for C$_{12}$H$_{16}$O$_6$ - H$_2$O: 378.24062; Found: 378.24059 (M$^+$ -H$_2$O).

**Syntheses of 15 and 16 from 14**

1$^\text{st}$ method. To a solution of 14 (165.7 mg, 0.42 mmol) in anhydrous \( \text{CH}_2\text{Cl}_2 \) (0.5 mL) at 0°C, anhydrous pyridine (40 µL, 0.96 mmol) and mesyl chloride (75 µL, 0.96 mmol) were added. After stirring for 1 h, the ice bath was removed and reaction mixture was stirred at room temperature for another 8 h. The mixture was diluted with EtOAc (10.0 mL) and washed successively with 5% HCl and saturated solutions of CuSO$_4$ and NaHCO$_3$. The organic layer was dried over anhydrous MgSO$_4$ and the solvent removed in a rotary evaporator. The residue was then dissolved in anhydrous benzene (11.0 mL) and DBU (0.16 mL, 1.1 mmol) was added. After refluxing for 48 h, the reaction mixture was cooled to room temperature and the solvent was evaporated to the dryness. The crude product was dissolved in EtOAc (20.0 mL) and was washed with water. The organic layer was dried over anhydrous MgSO$_4$ and the solvent was removed in a rotary evaporator. The residue was chromatographed on silica gel (n-hexane-EtOAc, 85:15) to furnish 15 and 16 (85.3 mg, 54%) in a ratio of 88:12, respectively.

2$^\text{nd}$ method. To a solution of 14 (73.0 mg, 0.19 mmol) in anhydrous petroleum ether:pyridine (1:1, 2.0 mL) under nitrogen atmosphere, a solution of POCl$_3$ (38 µL, 0.40 mmol) in anhydrous petroleum ether (1.0 mL) was slowly added. After refluxing for 48 h, the mixture was cooled to room temperature and the solvent was evaporated to the dryness. The crude product was dissolved in EtOAc (2 x 10.0 mL) and the solution was extracted with water. After refluxing for 48 h, the reaction mixture was cooled to room temperature and the solvent was evaporated to the dryness. The crude product was redissolved in EtOAc (20.0 mL) and was washed with water. The organic layer was dried over anhydrous MgSO$_4$ and the solvent was removed in a rotary evaporator. The residue was chromatographed on silica gel (n-hexane-EtOAc, 85:15) to furnish 15 and 16 (23.0 mg, 33%) as colorless oil in a ratio of 88:12, respectively.
(C-17), 25.7 (C-11), 27.0 (C-12), 34.6 (C-10), 36.7 (C-3), 37.6 (C-1), 41.2 (C-5), 46.4 (C-4), 52.0 (C-21), 52.1 (C-22), 53.5 (C-9), 57.2 (C-7), 58.8 (C-8), 125.2 (C-13), 132.2 (C-15), 170.6 (C-14), 176.2 (C-18); For compound 16:

1H NMR (500 MHz) δ: 0.93 (s, 3H, H-20), 0.94 (d, J 6.0 Hz, 6H, H-16, H-17); 0.95 (m, 1H, H1), 1.22 (s, 3H, H-19), 1.421.60 (m, 4H, H-2, H-2'), 1.63-1.90 (m, 5H, H-5, H-6), 2.22 (sept, J 6.5 Hz, 1H, H-15), 2.37 (dd, J 12.0, 7.2 Hz, H-12), 3.16 (m, 1H, H-10), 3.18 (m, 1H, H-9), 3.65 (s, 3H, H-21), 3.66 (s, 3H, H-22), 5.25 (ddd, J 5.0, 14.8, 6.0 Hz, 1H, H-1), 5.41 (dd, J 15.8, 6.0 Hz, 1H, H-13);

13C NMR (125 MHz) δ: 14.8 (C-20), 17.0 (C-19), 17.7 (C-2), 22.3 (C-16), 22.4 (C-17), 23.7 (C-6), 23.8 (C-11), 31.2 (C-15), 34.6 (C-10), 36.7 (C-3), 37.6 (C-1), 41.2 (C-5), 46.4 (C-4), 52.0 (C-21), 52.1 (C-22), 53.5 (C-9), 57.2 (C-7), 58.9 (C-8), 123.7 (C-12), 139.8 (C-13), 170.6 (C-14), 178.2 (C-18); HRMS: Calcd. for C_{12}H_{20}O_{6}: 378.24062; Found: 378.24157 (M⁺).

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