Communication

Dimethyl 2-[[2-(2-Methoxy-1-methoxycarbonyl-2-oxoethyl)-4,5,7-trimethoxy-3-(2,4,5-trimethoxyphenyl)-2,3-dihydro-1H-inden-1-yl]methyl]malonate

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Abstract: A simple synthetic approach to dimethyl 2-[[2-(2-methoxy-1-methoxycarbonyl-2-oxoethyl)-4,5,7-trimethoxy-3-(2,4,5-trimethoxyphenyl)-2,3-dihydro-1H-inden-1-yl]methyl]malonate has been developed, based on a B(C_6F_5)_3-induced domino dimerization of 2-(2,4,5-trimethoxyphenyl)cyclopropane-1,1-diester.

Keywords: donor–acceptor cyclopropane; 2,3-dihydro-1H-indene; dimerization reaction; domino process

1. Introduction

Donor–acceptor (D–A) cyclopropanes [1–3] have proven themselves as unique substrates containing multiple reaction centers, that allow them to participate in a broad variety of transformations including unusual ones, such as diverse dimerization reactions [4–6]. The cyclodimerization reactions of (D–A) cyclopropanes represent an efficient way to significantly increase the structural complexity of a substrate in a single synthetic step and can provide straightforward routes to complex polycyclic compounds. Various cyclodimerizations, reported to date, can be divided into three main groups: (1) (3 + 3)-cyclodimerizations affording cyclohexane, 1,2,3,4-tetrahydronaphthalene or 9,10-dihydroanthracene derivatives and their heterocyclic analogues [7–10]; (2) (3 + 2)-cyclodimerization leading to aryldienes, dialkyldipentanes, etc. [9–14]; (3) other types of cyclodimerizations [10,15–20]. The chemoselectivity of the cyclodimerizations is guided by both the nature of the substituents in the starting D–A cyclopropane and the choice of a suitable Lewis acid. Among the disclosed dimerization processes, one should note the cyclopropane-to-indane transformation as an analogue of styrene- and stilbene-based biosynthesis of indane structures, such as diisoeugenol, pallidol, griffipavixinanthone, laetevirenol A, quadrangularin A, parthenocissin A, parvifolol (Figure 1) exhibiting cytotoxic [21,22], antioxidant [21,23–26], and other [25–27] activities.
In line with our ongoing research related to D–A cyclopropane dimerizations [7,8,11–14,20], herein, we report the synthesis of polyoxygenated indane 1, which is a structural analog of diazarone, via a B(C6F5)3-induced (3 + 2)-cyclodimerization of 2-(2,4,5-trimethoxyphenyl)cyclopropane-1,1-diester 2 in one step in highly chemo-, regio- and stereoselective manner.

2. Results and Discussion

Starting cyclopropane 2 was synthesized from commercial 2,4,5-trimethoxybenzaldehyde 3 via a two-step synthetic sequence which involves the Knövenagel condensation with dimethyl malonate to afford arylidenemalonate 4 followed by the Corey-Chaykovsky reaction (Scheme 1) [28].

The structure of 2,4,5-trimethoxyphenyl-substituted cyclopropane 2 was unambiguously confirmed by single crystal X-ray analysis (Figure 2) [29]. In general, the structure of cyclopropane 2 closely matches the structure of related 2-aryl cyclopropane-1,1-dicarboxylates described previously [30–32]. All of them have the same configuration of ester groups. The methoxycarbonyl group in the trans-position with respect to the donor aromatic substituent is located approximately along the bisector of the angle C(2)–C(1)–C(3) with the carbonyl oxygen atom directed towards the cyclopropane fragment, while the alkoxy group, respectively, in the opposite direction. The second ester group is usually arranged so that the carbonyl oxygen atom has an exo-location relative to the three-membered ring and the methoxy group is endo-located, the torsion angle between two ester groups being dependent on the nature of the cis-aromatic substituent.
In this paper, we studied the possibility of using B(C₆F₅)₃ as a catalyst of cyclopropane 2 dimerization accounting for fact that this reagent is referred to as an ideal boron Lewis acid [34]. Our preliminary studies revealed that the use of conventional Lewis acids (BF₃·Et₂O, SnCl₄) does not lead to satisfactory results as complex mixtures of dimeric products and products of oligomerization were obtained. After a short screening of the reaction conditions, we have found that the best yields are obtained after heating 2 M solution of 2 in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) in the presence of B(C₆F₅)₃ (10 mol %) under microwave irradiation at 58 °C for 7 h (Scheme 2).

![Scheme 2. Synthesis of dimer 1.](image)

According to nuclear magnetic resonance spectroscopy (NMR) data, the dimerization of cyclopropane 2 produced 1 as a mixture of two isomers in 84:16 ratio. The relative configuration of the major isomer of dimer 1 was assigned on the basis of 2D nuclear Overhauser effect spectroscopy (NOESY) experiments (Scheme 3). For major isomer the trans,trans-arrangement of substituents in five-membered ring was established. The minor isomer of 1 was determined to be the C-1 epimer, and its spectral parameters completely correspond to the literature data for the related dimers [12,13].

![Scheme 3. Representative NOE responses for the major isomer of 1.](image)

The predominant formation of trans,trans-isomer differs from the previously reported results on the exclusive formation of cis,trans-isomers of the related indanes in the cycldimerization of the D–A cyclopropanes [12,13]. Taking into account the cis,trans-geometry of the naturally occurring analog, diazarone, we believe that this reversal of stereoselectivity can be explained by the nature of bulky Lewis acid used in this study. Unlike SnCl₄ and BF₃, B(C₆F₅)₃ coordinates to an acceptor group in cyclopropane 2 in such a way, that attack of isomeric alkene 5, formed by an initial isomerization of 2, on cyclopropane results in an intermediate 6 with anti-arrangement of substituents at carbon atoms that form a new bond (Scheme 4). Cyclization of 6 proceeds under thermodynamic control and affords the most stable trans,trans-1.
In summary, the B(C₆F₅)₃-induced cyclodimerization of 2-(2,4,5-trimethoxyphenyl)cyclopropane-1,1-diester 2 provides a concise route to polyoxygenated indane 1, which is a structural analogue of diazarone and has a potential for pharmacological studies.

3. Materials and Methods

NMR spectra were acquired on Bruker AM-400 and Bruker Avance 600 spectrometers at room temperature; the chemical shifts δ were measured in ppm with respect to the solvent (¹H: CDCl₃, δ = 7.27 ppm; ¹³C: CDCl₃, δ = 77.0). The splitting patterns are designated as s, singlet; d, doublet; m, multiplet; dd, double doublet; br., broad. The coupling constants (J) were in Hertz. The ¹H-NMR, ¹³C-NMR, 2D heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond correlation (HMBC), nuclear Overhauser effect (NOESY) NMR spectra for the synthesized compound are available in the Supplementary Material. Infrared spectra were recorded on the Infralum FT-801 spectrometer. High resolution and accurate mass measurements were carried out using a micrOTOF-Q™ ESI-TOF (electro spray ionization/time of flight, Bruker, Billerica, MA, USA) and LTQ Orbitrap mass spectrometer (Thermo Fischer Scientific, Waltham, MA, USA). Elemental analyses were performed with an EA-1108 CHNS elemental analyzer instrument (Fisons, Ipswich, UK). X-ray analysis was performed on STOE STADIVARI PILATUS-100K diffractometer (Stoe & Sie, Darmstadt, Germany). The microwave reaction was performed in a Monowave 300–Anton Paar microwave reactor (Anton Paar GmbH, Graz, Austria) in sealed reaction vessels. The temperature was monitored with the installed IR detector. The melting points (m.p.) were determined using a 9100 capillary melting point apparatus (Electrothermal, Stone, UK). Analytical thin layer chromatography (TLC) was carried out with silica gel plates (silica gel 60, F₂₅₄, supported on aluminum); the revelation was done by UV lamp (365 nm). Column chromatography was performed on silica gel 60 (230–400 mesh, Merck, Darmstadt, Germany). All reactions were carried out using freshly distilled and dry solvents. Commercial reagents employed in the synthesis were analytical grade, obtained from Aldrich (St. Louis, MI, USA) or Alfa Aesar (Ward Hill, MO, USA). CCDC 1972617 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk).

Scheme 4. The proposed mechanism of dimer 1 formation.
3.1. Dimethyl 2-(2,4,5-trimethoxybenzylidene)malonate (4)

To a solution of 2,4,5-trimethoxybenzaldehyde (5 g, 25.5 mmol) and dimethyl malonate (2.92 mL, 25.5 mmol) in toluene (8.5 mL), glacial acetic acid (292 µL, 5.1 mmol) and pipiderine (252 µL, 2.55 mmol) were added. The mixture was refluxed with the Dean-Stark trap until water separation was finished (1 h). Upon cooling, the organic layer was washed with water (3 × 10 mL), dried with Na₂SO₄, concentrated in vacuo. The purification by flash chromatography (SiO₂) afforded target alkenes 4.

¹H NMR (CDCl₃, 400 MHz): δ = 3.74 (s, 3H, CH₂O), 3.77 (s, 6H, 2 × CH₃O), 3.79 (s, 3H, CH₂O), 3.86 (s, 3H, CH₃O), 6.43 (s, 1H, Ar), 6.89 (s, 1H, Ar), 8.03 (s, 1H, CH=). ¹³C NMR (CDCl₃, 100 MHz): δ = 52.2 (2 × CH₂O), 55.9 (CH₂O), 56.2 (2 × CH₃O), 96.5 (CH Ar), 111.6 (CH Ar), 113.2 (C Ar), 122.3 (C Ar), 137.8 (CH=, Ar), 143.0 (C Ar), 152.7 (C Ar), 154.1 (C Ar), 165.0 (CO₂Me), 167.8 (CO₂Me). IR (KBr): ν = 3006, 2948, 1726, 1710, 1596, 1599, 1522, 1478, 1469, 1446, 1434, 1237, 1224, 1209, 1189, 1175, 1131, 1069, 1047 cm⁻¹. HRMS ESI-TOF: m/z = 333.0944 [M + Na]+ (333.0945 calcd for C₁₅H₁₈NaO₇).

3.2. Dimethyl 2-(2,4,5-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate (2)

To dry DMF (14 mL) NaH (60% suspension in oil, 329 mg, 8.2 mmol) and trimethylsulfoxonium iodide (1.81 g, 8.2 mmol) were successively added in a single portion under argon atmosphere at room temperature. Vigorous evolution of hydrogen lasted ca. 10 min, after which the reaction mixture was stirred for additional 30 min. Dimethyl 2-(2,4,5-trimethoxybenzylidene)malonate (2.22 g, 6.9 mmol) in dry DMF (2 mL) was added in portions. The resulting mixture was stirred for 2 h, poured into ice-cooled aq. solution of NH₄Cl (25 mL) and extracted with ethyl acetate (5 × 10 mL). The combined organic fractions were washed with water (5 × 10 mL), dried with Na₂SO₄ and concentrated in vacuo. The resulting residue was purified by recrystallization from Et₂O yielding cyclopropane 2. Yield 1.38 g (60%); white solid; mp 109–110 °C. ¹H NMR (CDCl₃, 400 MHz): δ = 1.71 (dd, 2J = 5.2 Hz, 3J = 9.4 Hz, 1H, CH₂), 2.13 (dd, 2J = 8.4 Hz, 1H, CH₂), 2.36 (dd, 2J = 9.4 Hz, 3J = 8.4 Hz, 1H, CH), 3.37 (s, 3H, CH₂O), 3.76 (s, 3H, CH₃O), 3.77 (s, 6H, 2 × CH₃O), 3.84 (s, 3H, CH₂O), 6.45 (s, 1H, Ar), 6.50 (s, 1H, Ar). ¹³C NMR (CDCl₃, 100 MHz): δ = 19.0 (CH₂), 28.3 (CH), 36.2 (C), 52.0 (CH₂O), 52.5 (CH₂O), 55.8 (CH₂O), 56.40 (CH₃O), 97.1 (CH Ar), 111.9 (CH Ar), 114.1 (C Ar), 142.2 (C Ar), 148.8 (C Ar), 153.5 (C Ar), 167.2 (CO₂Me), 170.3 (CO₂Me). IR (KBri): ν = 2926, 2950, 2841, 1721, 1515, 1471, 1440, 1431, 1401, 1318, 1294, 1276, 1211, 1123, 1030 cm⁻¹. HRMS ESI-TOF: m/z = 347.1098 [M + Na]+ (347.1101 calcd for C₁₆H₂₀NaO₂). Anal. calcd for C₁₆H₂₀O₂: C, 59.25; H, 6.22. Found: C, 59.16; H, 6.05. Crystal Data for C₁₆H₂₀O₂ (M = 324.32 g/mol): triclinic, space group P-1 (no. 2), a = 8.7161(3) Å, b = 9.1767(3) Å, c = 10.0231(3) Å, α = 90.334(2)°, β = 93.435(2)°, γ = 95.415(2)°, V = 795.77(4) Å³, Z = 2, T = 295 K, μ(CuKα) = 0.090 mm⁻¹. Dcalc = 1.354 g/cm³, 16,914 reflections measured (4.424° ≤ θ ≤ 73.202°), 3012 unique (Rint = 0.0419, Rsigma = 0.0531) which were used in all calculations. The final R₁ was 0.0494 ([L > 2σ(L)]) and wR₂ was 0.1471 (all data).

3.3. Dimethyl 2-[[2-(2-methoxy-1-methoxycarbonyl-2-oxoethyl)-4,5,7-trimethoxy-3-(2,4,5-trimethoxyphenyl)-2,3-dihydro-1H-inden-1-yl]methyl]malonate (1) (as a mixture of (1RS,2RS,3RS)- and (1RS,2SR,3SR)-isomers in 84:16 Ratio)

A dry reaction microwave tube was charged with cyclopropane 2 (150 mg, 0.46 mmol) and HFIP (0.23 mL) under N₂ atmosphere. B(C₆F₅)₃ (24 mg, 0.046 mmol) was added and the reaction mixture was heated in a microwave reactor at 58 °C for 7 h, quenched with conc. aqueous NaHCO₃ and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with NaHCO₃ and brine, dried with anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography on a silica gel to afford the desired product. Yield 129 mg (86%); colorless oil; Rf = 0.81 (petroleum ether:ethyl acetate; 1:1); mixture of diastereomers ([1RS,2RS,3RS]-1:[1RS,2SR,3SR]-1 in 84:16 ratio). (1RS,2RS,3RS)-1: ¹H NMR (CDCl₃, 600 MHz): δ = 2.00–2.07 (m, 2H, C(1′)H₂), 2.66 (d, 3J₁,₂ = 8.0 Hz, 1H, C(1')H), 3.16 (t, 3J = 7.6 Hz, 1H, C(1'H), 3.47 (s, 3H, CH₃O), 3.51 (s, 3H, CH₂O), 3.56 (br, d, 3J₁,₂ = 8.0 Hz, 1H, C(2'H), 3.60 (s, 3H, CH₃O), 3.61 (s, 3H, CH₂O), 3.61–3.63 (m, 1H, C(2')H), 3.64 (s, 3H, CH₂O), 3.745 (s, 3H, CH₃O), 3.752 (s, 3H, CH₂O), 3.82 (s, 3H, CH₂O), 3.847 (s, 3H, CH₂O),
Acknowledgments: The following are available online, Figure S1: $^1$H NMR spectrum of 4; Figure S2: $^{13}$C NMR spectrum of 4; Figure S3: $^1$H NMR spectrum of 2; Figure S4: $^{13}$C NMR spectrum of 2; Figure S5: $^1$H NMR spectrum of 1; Figure S6: $^{13}$C NMR spectrum of 1; Figure S7: HSQC $^1$H-$^{13}$C spectrum of 1; Figure S8: HMBC $^1$H-$^{13}$C spectrum of 1; Figure S9: NOESY $^1$H-$^1$H spectrum of 1.

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References


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