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Short Note

2-(*tert*-Butyl)-4-phenyloxetane

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Abstract: The two geometric isomers of 2-(*tert*-butyl)-4-phenyloxetane have, for the first time, been prepared starting from the commercially available 4,4-dimethyl-1-phenylpentane-1,3-dione. The latter was reduced with $NaBH_4$ to give a mixture of diastereomeric *syn* and *anti* diols which were then stereospecifically cyclized into the corresponding oxetanes with an overall yield for the two steps of 69.6%. The newly synthesized stereoisomeric four-membered oxygenated heterocycles were separated by column chromatography on silica gel and fully spectroscopically characterized.

Keywords: oxetanes; diols; diastereoisomers; cyclization reactions; NMR; heterocycles

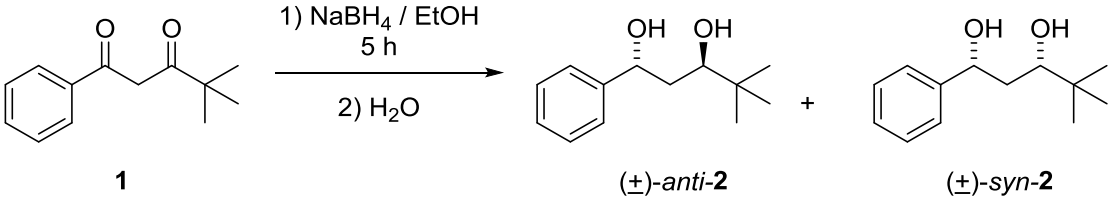
1. Introduction

Oxetanes are an important group of four-membered heterocyclic compounds that have recently received a great deal of attention as useful tools for both drug discovery and organic synthesis [1]. The oxetane motif is also ubiquitous in many natural products (e.g., taxol, oxetanocin, mitrophorone) [2–4] and is widely used in the medicinal chemistry for fine-tuning the physicochemical and hydrophilic properties of (biological active) organic compounds; it is also used as an isosteric replacement of both the carbonyl and the gem-dimethyl groups [5]. In addition, oxetanes are versatile templates for the construction of valuable heterocyclic compounds and several chiral synthons by ring expansion, ring opening, rearrangement and desymmetrization reactions [6–9].

The employment of these compounds in organic synthesis has progressively increased, particularly in the last 15 years, with the development of new and more efficient methods for their preparation. Nowadays, photochemical Paternò–Büchi [2+2] reactions of carbonyl compounds with alkenes [10], intramolecular Williamson etherification [11] and ring expansion of epoxides with sulfoxonium ylides [12] are already established general methods for their synthesis. More functionalized derivatives can be prepared by regioselective lithiation-electrophilic trapping processes starting from 2-aryloxetanes, 2-sulphonyloxetanes and hydrazones of oxetan-3-one [13–17]. The synthesis of stereodefined 2,4-disubstituted oxetane scaffolds still remains a challenge in contemporary organic synthesis. Inspired by a work of Nelson and co-workers [18,19], our group has recently reported on the preparation of 2,4-disubstituted aryloxetanes in an enantioenriched form [20], exploiting as a key step a stereoselective biocatalytic reduction of diketones to optically active β-aldols using wild-type whole cell biocatalysts (e.g., thermotolerant *Kluyveromyces marxianus* yeast and the *Lactobacillus reuteri* strain [21–23]). Building on this finding, in this short note we describe the preparation and the structural characterization of stereodefined and sterically demanding *cis*- and *trans*-2-(*tert*-butyl)-4-phenyloxetanes.

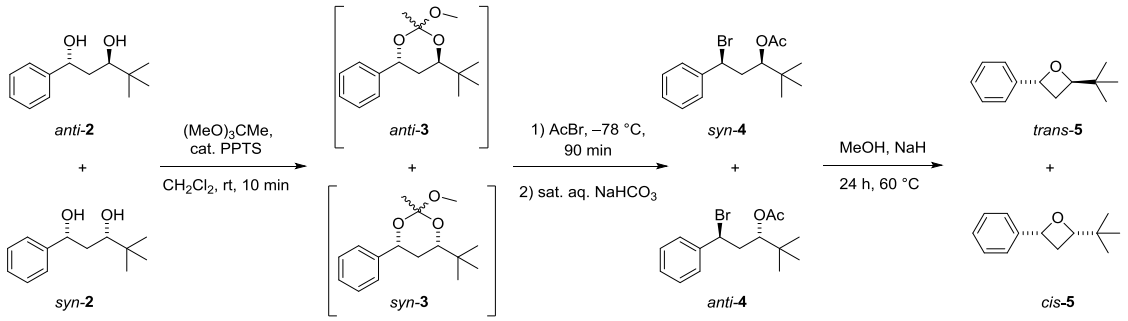
2. Results and Discussion

As a first step of the synthesis procedure, the commercially available 4,4-dimethyl-1-phenylpentane-1,3-dione **1** was reduced with $NaBH_4$ in EtOH to give an almost equimolar mixture [diastereomeric ratio (dr): 57:43] of the two diastereomeric *syn*- and *anti*-**2** diols in an overall yield of 94% (Scheme 1).



Scheme 1. Synthesis of *anti*- and *syn*-4,4-dimethyl-1-phenylpentane-1,3-diols (**2**).

The latter could then be stereospecifically cyclized into the corresponding 2,4-disubstituted aryloxetanes according to a two-step procedure reported by Nelson [18,19]. In the first step, the mixture of diastereomeric diols was preliminary converted into orthoesters **3** by reaction with trimethyl orthoacetate, followed by treatment with acetyl bromide and quenching by a saturated aqueous solution of $NaHCO_3$ to give the bromoacetate intermediates **4** (Scheme 2). In the next step, the crude mixture of acetates **4** was subjected to methanolysis and ring closure promoted by NaH/THF, thereby providing both *trans*- and *cis*-2-(*tert*-butyl)-4-phenyloxetanes (**5**). The overall transformation of diols into oxetanes was found to proceed via two stereospecific inversion reactions, and thus with the overall retention of the configuration at the two stereogenic centers: *anti*-diol **2** led to oxetane *trans*-**5**, whereas *syn*-diol **2** furnished oxetane *cis*-**5**, the final dr (55:45, determinated by ^{1}H-NMR analysis of the crude) mirroring that of the starting diols *anti*- and *syn*-**2**. The two geomeric isomers were finally separated and purified by silica gel column chromatography: *trans*-**5**: 39% yield; *cis*-**5**: 35% yield.



Scheme 2. Cyclization reaction of diols *anti*-**2** and *syn*-**2** into oxetanes *trans*-**5** and *cis*-**5**, respectively.

The relative configuration of oxetanes *trans*-**5** and *cis*-**5** was established by phase-sensitive 2D-NOESY spectra whose cross-peaks are diagnostic of a spatially close hydrogen relationship. As for the major diastereoisomer, significant NOE interactions were detected between protons H^1 and H^3, H^2 and $H^{3'}$, and between protons of the *tert*-butyl group and H^1, which are consistent with a *trans* arrangement of the phenyl and *tert*-butyl groups (Figure 1). In the case of the minor diastereoisomer, NOE interactions between proton H^3 and both protons H^1 and H^2 are consistent with a *cis* arrangement of the phenyl and *tert*-butyl groups instead (Figure 2).

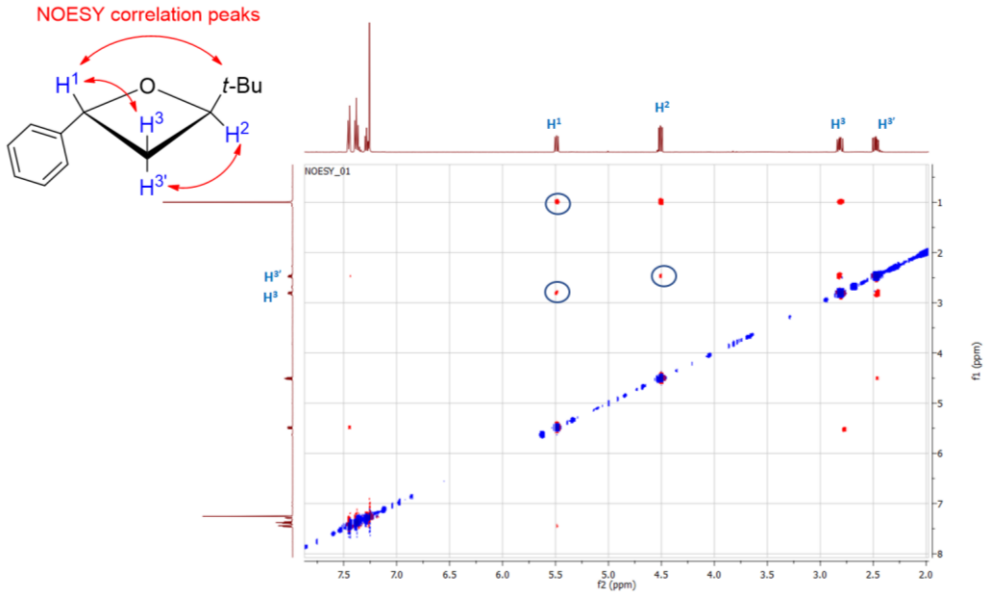


Figure 1. 2D-NOESY NMR spectrum, $CDCl_3$, *trans*-2-(*tert*-butyl)-4-phenyloxetane (**5**): selected NOE interactions.

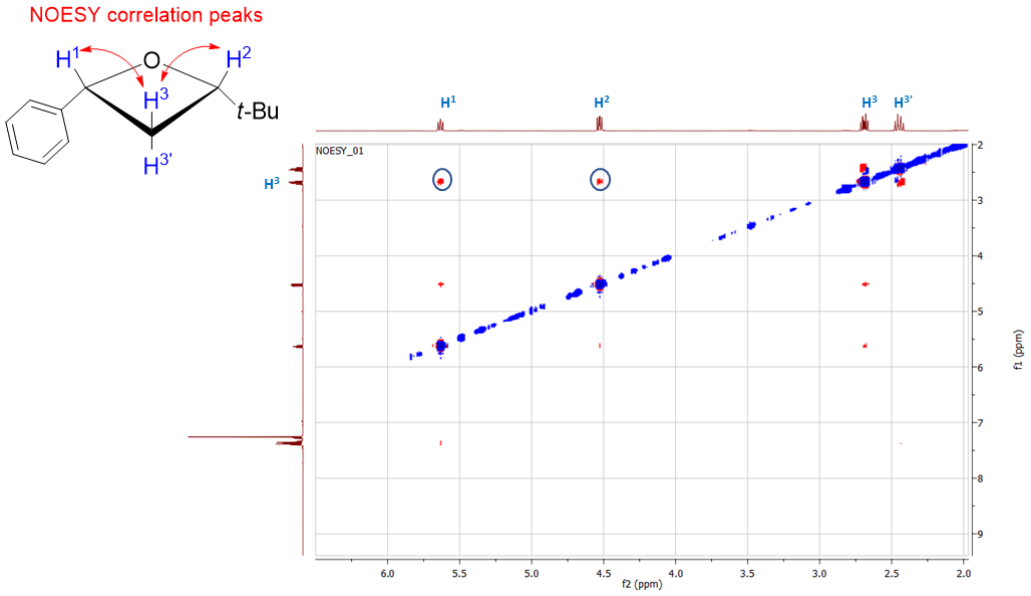


Figure 2. 2D-NOESY NMR spectrum, $CDCl_3$, *cis*-2-(*tert*-butyl)-4-phenyloxetane (**5**): selected NOE interactions.

3. Materials and Methods

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 600 MHz (Bruker, Milan, Italy) or on a Varian Inova 400 MHz spectrometer (Agilent Technologies, Santa Clara, CA, USA) and chemical shifts are reported in parts per million (δ). Absolute values of the coupling constants are reported. FT-IR spectra were recorded on a Perkin-Elmer 681 spectrometer (Perkin Elmer, Waltham, MA, USA). GC analyses were performed on a HP 6890 model, Series II by using a HP1 column (methyl siloxane; 30 m × 0.32 mm × 0.25 µm film thickness). Analytical thin-layer chromatography (TLC) was carried out on pre-coated 0.25-mm-thick plates of Kieselgel 60 F254; visualisation was accomplished by UV light (254 nm) or by spraying a solution of 5 % (*w*/*v*) ammonium molybdate and 0.2 % (*w*/*v*) cerium(III) sulfate in 100 mL 17.6 % (*w*/*v*) aq. sulfuric acid and heating to 473 K until blue spots appeared. Chromatography was conducted by using silica gel 60 with a particle size distribution 40–63 µm and 230–400 ASTM. GC-MS analyses were performed on a HP 5995C model (Agilent Technologies,

Santa Clara, CA, USA). The high resolution mass spectrometry (HRMS) analyses were performed using a Bruker microTOF QII mass spectrometer (Bruker, Milan, Italy) equipped with an electrospray ion source (ESI) operating in positive ion mode.

3.1. Synthesis of anti- and syn-4,4-dimethyl-1-phenylpentane-1,3-diols **2**

To a solution of 4,4-dimethyl-1-phenylpentane-1,3-dione (**1**) (408 mg, 2 mmol) in EtOH (4 mL), stirred at 0 °C, $NaBH_4$ (171 mg, 4.5 mmol) was added. After 16 h, water was added and the aqueous solution extracted with EtOAc. The residue was purified by silica gel column chromatography using hexane and EtOAc (80:20) as the eluents to yield 94% of *anti-* and *syn-* 4,4-dimethyl-1-phenylpentane-1,3-diols **2**; dr *anti*/*syn* = 57:43.

Anti- and syn-4,4-Dimethyl-1-phenylpentane-1,3-diols (*anti*-**2** and *syn*-**2**). Inseparable mixture of diastereoisomers, colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39–7.27 (m, 5 H major stereoisomer + 5 H minor stereoisomer, aromatic protons), 5.10–5.04 (m, 1 H minor, CH(OH)), 4.95–4.88 (m, 1 H, major, CH(OH)), 3.64–3.56 (m, 1 H, major, CH(OH)), 3.54–3.47 (m, 1 H, minor, CH(OH)), 3.00–2.74 (bs, 1 H major + 1 H minor, OH, exchanges with D_2O), 2.05–1.58 (m, 2 H major + 2 H minor, CH_2 and 1 H major + 1 H minor, OH, exchange with D_2O), 0.90 (s, 9 H, major), 0.87 (s, 9 H, minor); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 144.7 (major stereoisomer), 144.6 (minor stereoisomer), 128.45 (major), 128.38 (minor), 127.5 (major), 127.1 (minor), 125.7 (major), 125.4 (minor), 80.9 (major), 76.2 (minor), 72.2 (minor), 71.9 (major), 40.0 (major), 39.3 (minor), 34.9 (minor), 34.6 (major), 25.5 (major), 25.4 (minor); FT IR (neat): 3370, 3089, 3063, 3038, 2957, 2870, 1454, 1393, 1365, 1323, 1208, 1175, 1057, 1014, 853, 759, 700 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{13}H_{20}NaO_2$: 231.1361; Found: 231.1356.

3.2. Synthesis of trans- and cis-2-(tert-Butyl)-4-phenyloxetanes **5**

Trimethyl orthoacetate (553 μL, 3.6 mmol) and pyridinium toluene-*p*-sulfonate (8 mg) were added to a stirred solution of diols *anti*-**2** and *syn*-**2** (624 mg, 3 mmol) in dry CH_2Cl_2 (30 mL). The reaction mixture was stirred for 10 min at room temperature, cooled to −78 °C, and acetyl bromide (631 μL, 7.2 mmol) was added. The reaction was stirred for an additional 1.5 h, quenched with sat. aq. $NaHCO_3$ solution, extracted with CH_2Cl_2 (3 × 20 mL), dried (Na_2SO_4), filtered and evaporated to give a crude product. The latter was dissolved in dry THF (30 mL), and MeOH (138 μL, 4.1 mmol) and NaH (444 mg, 60% dispersion in oil, 9.1 mmol) were sequentially added. The vessel was sealed with a glass cap and the reaction stirred for 24 h at 60 °C. After this time, the reaction was quenched with water and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to give a crude product which was purified by flash silica gel column chromatography (10% Et_2O in hexane), to give *trans*- and *cis*-2-(*tert*-butyl)-4-phenyloxetanes **5**.

trans-2-(tert-Butyl)-4-phenyloxetane (*trans*-**5**): 39% yield, waxy solid, R_f = 0.6. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.47–7.44 (m, 2 H, aromatic protons), 7.40–7.37 (m, 2 H, aromatic protons), 7.31–7.27 (m, 1 H, aromatic proton), 5.49 (dd, 1 H, *J* = 8.6, 6.4 Hz, CH(OH)), 4.51 (dd, 1 H, *J* = 8.5, 6.4 Hz, CH(OH)), 2.84–2.79 (m, 1 H, CH_2), 2.51–2.45 (m, 1 H, CH_2), 1.00 (s, 9 H, *t*-Bu); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 140.8, 128.4, 127.5, 125.5, 125.3, 85.7, 79.9, 30.7, 29.7, 23.8; GC MS (70 eV) *m*/*z* (%): 190 (13), 134 (13), 133 (7), 107 (22), 106 (10), 105 (100), 104 (78), 103 (36), 92 (28), 91 (10), 84 (86), 79 (18), 78 (35), 77 (45), 69 (69), 57 (73), 51 (14), 43 (10), 41 (35); FT-IR (neat): 2954, 2923, 2855, 1650, 1458, 1100, 1030, 980, 749, 696 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{13}H_{18}NaO^+$: 213.1250; Found: 213.1255.

cis-2-(tert-Butyl)-4-phenyloxetane (*cis*-**5**): 35% yield, waxy solid, R_f = 0.5. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.41–7.33 (m, 4 H, aromatic protons), 7.29–7.26 (m, 1 H, aromatic proton), 5.65–5.62 [m, 1 H, CH(OH)], 4.54–4.52 (m, 1 H, CH(OH)), 2.72–2.66 (m, 1 H, CH_2), 2.47–2.43 (m, 1 H, CH_2), 0.92 (s, 9 H, *t*-Bu); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 144.9, 128.3, 127.4, 125.5, 125.3, 85.0, 76.6, 31.5, 29.7, 24.2; GC MS (70 eV) *m*/*z* (%): 190 (10), 175 (5), 134 (4), 133 (4), 107 (33), 105 (75), 104 (76), 103 (36), 92 (16), 84 (97), 79 (18), 78 (34), 45 (77), 69 (100), 57 (50), 51 (14), 43 (10), 41 (37); FT-IR (neat): 2955, 2925, 2853, 1651, 1462,

1110, 1032, 982, 752, 697 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for: $C_{13}H_{18}NaO^+$ 213.1250; Found: 213.1247.

4. Conclusions

In summary, both geometric isomers of *trans*- and *cis*-2-(*tert*-butyl)-4-phenyloxetane have, for the first time, been synthesized. The overall transformation involves the following steps: (a) reduction of the commercially available 4,4-dimethyl-1-phenylpentane-1,3-dione with $NaBH_4$ to give an almost equimolar mixture of inseparable diastereomeric 1,3-diols, and (b) a one-pot, two-step stereospecific cyclization of *syn*- and *anti*-diols into the corresponding 2,4-disubstituted aryloxetanes, which could be finally separated by column choromatography and spectroscopically characterized. The corresponding enantiomerically enriched diastereomers could not be prepared via a chemoenzymatic route, as analogously done with other 2,4-disubstituted aryl derivatives [20]. In fact, no reduction was noticed when **1** was incubated in the presence of baker's yeast whole cells or *Lactobacillus reuteri* DSM 20016 resting cells, and the starting 1,3-dione was quantitatively recovered. The stereoselective bioreduction of sterically demanding bulky-bulky aryl alkyl ketones by conventional whole cells has always been, indeed, quite challenging [24]. The low solubility of **1** in aqueous solutions may have contributed as well to the failure of the enzymatic activity. Thus, future work will be focused on the preparation of densely substituted stereodefined oxetanes by exploiting dynamic resolution strategies starting from racemic α-lithiated aryloxetanes and chiral ligands [25,26]. Results will be reported in due course.

Supplementary Materials: ^1H and ^{13}C-NMR spectra of diol **2** and oxetanes *trans*-**5** and *cis*-**5** are available online.

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Author Contributions: F.M.P. and P.V. conceived and designed the experiments; S.S. performed the experiments; all authors analyzed the data; F.M.P., P.V. and V.C. contributed reagents/materials/analysis tools; F.M.P. and V.C. wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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