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A diastereoselective total synthesis of the sesquiterpene (±)-mutisianthol

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Abstract—The total synthesis of the phenolic sesquiterpene mutisianthol has been accomplished in 12 steps from the readily available 2-methylanisole. The required *trans*-1,3-disubstituted indan intermediate was obtained through a diastereoselective thallium(III) mediated ring contraction of a 1-methyl-1,2-dihydronaphthalene derivative.

1. Introduction

Structurally diverse indans have continuously been isolated along the years,[1,2] yielding new challenges to organic synthesis. Recent examples are fredericamycin,[3] which exhibits a potent antitumor activity, as well as the architecturally complex alkaloid (+)-ribasine.[4]

The phenolic sesquiterpene mutisianthol is also a member of this class of compounds. Such a molecule has been isolated by Bohlmann and co-workers in 1979, from the roots of *Mutisia homoeantha*.[5] Based on the spectroscopic data, the structure of this natural indan was assigned as **1**, which embodies a *cis*-1,3-disubstituted cyclopentyl unit. After nearly two decades of the work of Bohlmann, Ho and his group[6] reported a total synthesis of mutisianthol. In the first route, the authors obtained the acetylated *cis*-indan 2, whose structure is very similar to 1. However, comparing the NMR spectra of this intermediate with those of the natural compound, the authors considered that the relative configuration of mutisianthol could be *trans*. Eventually, a new route has been elaborated to give, in 12 steps from 3-*p*-tolylbutyric acid, the *trans* diastereomer of **1**, which shows identical spectroscopic data to the natural compound. Thus, Ho and co-workers proposed that the correct structure for mutisianthol should be **3** (Fig. 1).

Oxidative rearrangements promoted by thallium(III) have been applied in the ring contraction of olefins and of ketones.[7,8] In a previous paper, we described that the oxidation of 1-methyl-1,2-dihydronaphthalene with thallium trinitrate (TTN) furnishes, in excellent isolated yield, a ring contraction product, which exhibits a *trans*-relationship between the substituents of the cyclopentyl unit.[9] Recently, such a reaction has been used in a six step route to transform 6-methoxy-1-tetralone into an indan derivative related to the sesquiterpene mutisianthol and its isomer jungianol.[10,11]

Based on these studies, we decided to undertake a new total synthesis of mutisianthol. The proposed strategy centers on a thallium(III) promoted ring contraction to achieve the indan ring, as shown in the retrosynthetic sequence depicted in Scheme 1. It was anticipated that the target molecule (**3**) could be obtained, by an appropriate Wittig reaction, from the aldehyde formed by hydrolysis of the acetal **4**. The key intermediate **4** would be prepared by an oxidative

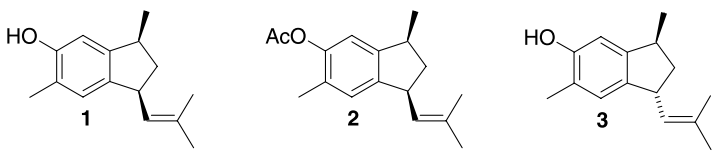

Figure 1. Structure of mutisianthol and related indans.

Keywords: indan; total synthesis; ring contraction; thallium(III).
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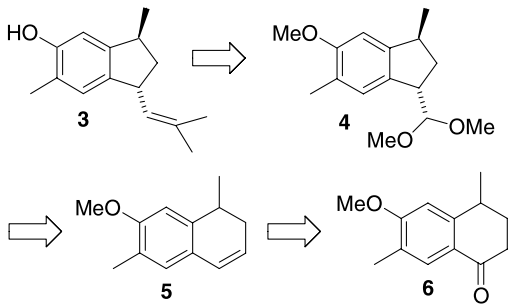


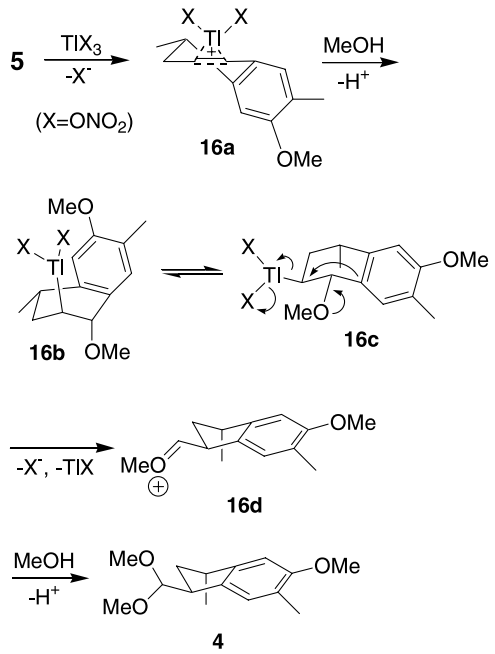
Scheme 1.

rearrangement of the dihydronaphthalene **5**, promoted by TTN. Through a few classical reactions, the olefin **5** could be achieved from the tetralone **6**.

2. Results and discussion

Our initial efforts focused on obtaining the tetralone **6**, which has already been prepared by Ayyangar and co-workers[12] in 6 steps. Utilizing this procedure, the commercially available and cheap 2-methylanisole (**7**) was transformed into tetralone **6**, as shown in Scheme 2. In some steps, the procedure described in the literature was slightly modified. Thus, the reduction of the keto-acid **8** under Clemmensen's conditions was realized using zinc amalgam.[13] The reaction of **10** with methyl magnesium iodide, followed by work-up with 10% aqueous solution of HCl (instead of 50% H_2SO_4), afforded the corresponding alkene **11** in slightly higher yield.

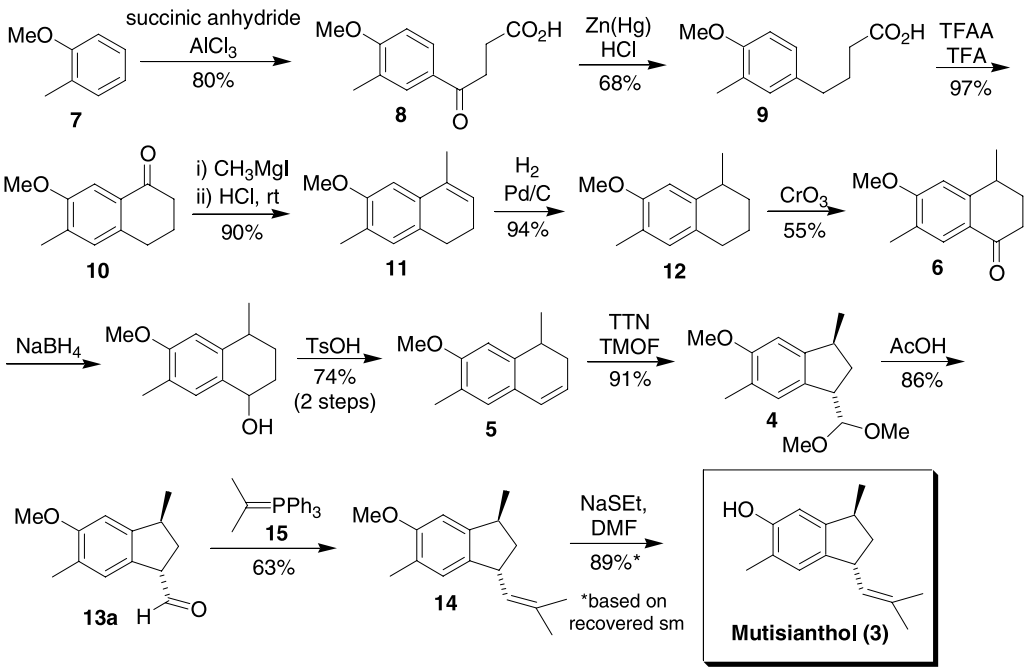
The next step was the reduction of tetralone **6**, which was best carried out using $NaBH_4$ in a mixture of MeOH and THF.[14] The crude tetralol was submitted to treatment with TsOH in benzene, to afford the required 1,2-dihydronaphthalene **5**. Subsequently, this intermediate was treated with TTN, providing the *trans*-1,3-disubstituted indan **4** in excellent yield.



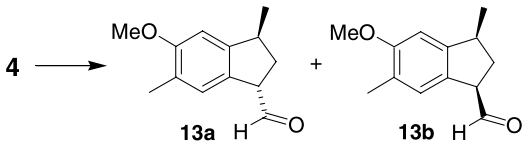
Scheme 3.

The formation of the *trans* diastereomer can be explained by the mechanism shown in Scheme 3. Ring-opening of the thallonium ion **16a**, in a Markovnikov sense, leads to the *trans*-diaxial oxythallated adduct **16b**, which undergoes a ring conformation inversion to **16c**, with the required anti-periplanarity for the rearrangement. Finally, the ring contraction product **4** is obtained through the intermediate **16d**, where the two substituents are in a *trans*-relationship.

Hydrolysis of the acetal **4** with trifluoroacetic acid,[15] as



Scheme 2.



Scheme 4.

previously described in the model studies,[10] gave a 7:2 diastereomeric mixture of the *trans* and *cis* aldehydes **13a** and **13b**, respectively, in 79% yield. Using Amberlyst-15,[16] a mixture of the epimers **13a** and **13b** was also obtained (Scheme 4). This epimerization was finally circumvented utilizing acetic acid, which furnished the desired aldehyde **13a** in good yield (see Scheme 2). In such a case only traces of the *cis* diastereomer have been observed.

Analyzing the NMR data for a series of substituted indans in the literature,[9,17–20] it was possible to note that *trans*-1-substituted-3-methyl indans can be distinguished from the corresponding *cis* isomers by ^{1}H NMR, because the hydrogens of the methyl group are shielded in *trans* isomers, when compared to the corresponding *cis* compounds. Moreover, analysis of the ^{13}C NMR data shows that the methyl group is slightly deshielded in *trans* isomers. Using these information, the assignment of the *cis*- and *trans*-aldehydes **13a** and **13b** could be made unequivocally, thus allowing to confirm our assignment for the key intermediate **4** (Fig. 2).

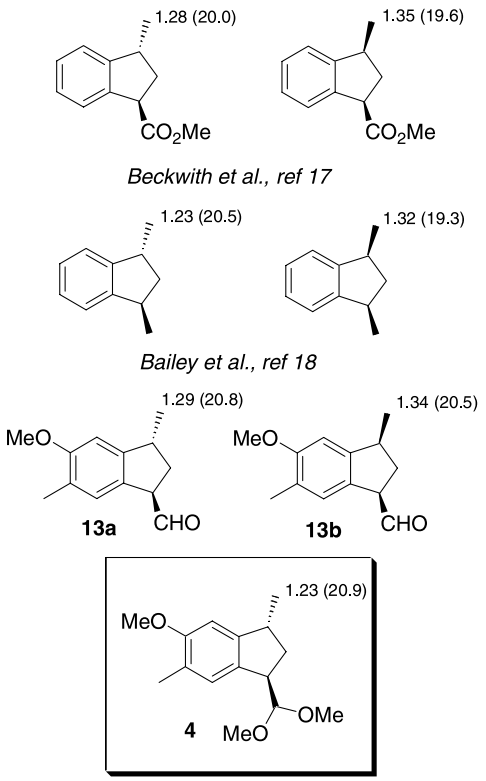


Figure 2. Selected ^{1}H and ^{13}C (in parentheses) NMR chemical shifts for some 1-substituted-3-methyl indans.

The last two steps of the synthesis could be performed under conditions similar to those used in the model studies. Thus, Wittig reaction[21] between the phosphorous ylide **15**[22] and the aldehyde **13a** allowed the introduction of the isopropenyl moiety of the target molecule, leading to **14**. Finally, deprotection of the methyl group with sodium ethanethiolate[23] gave mutisianthol (**3**) in good yield, as white needles.[24] The spectroscopic data of **3** agree with those reported earlier.[5,6]

In conclusion, a new total synthesis of mutisianthol was accomplished in 12 steps from the readily available 2-methylanisole. Our approach employs a diastereoselective thallium(III) mediated ring contraction to afford the 1,3-disubstituted indan **4** with the desired *trans* relative configuration. The application of a rearrangement reaction to get selectively an indan derivative has been reported only scarcely in the literature.[3] This approach represents, however, an efficient method to efficiently obtain cyclopentyl units, such as indans.[8] Having in mind the broad spectrum of biological activities of molecules bearing the indan skeleton, the compounds obtained in this study might exhibit some useful properties.

3. Experimental

3.1. General

Information concerning general experimental methods was recently published.[20] Warning! Thallium salts are toxic and must be handled with care.

3.1.1. 1,6-Dimethyl-7-methoxy-1,2-dihydronaphthalene (5). To a stirred solution of the tetralone **6**[12] (0.471 g, 2.31 mmol) in anhydrous THF (7 mL) and in anhydrous MeOH (10 mL), was added dropwise $NaBH_4$ (0.427 g, 11.3 mmol) at 0°C. The mixture was stirred for 1.5 h at room temperature. The reaction was quenched with H_2O (13 mL) and a 10% aqueous solution of HCl was added dropwise until pH around 5. The solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure giving a yellow oil that was diluted in benzene (17 mL). A few crystals of *p*-TsOH were added to this solution and the mixture was stirred for 1 h at room temperature. The organic phase was washed with 5% aqueous solution of $NaHCO_3$ (twice), with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure giving a yellow oil. The residue was purified by flash chromatography (silica gel 200–400 mesh, hexanes) affording **5** (0.319 g, 1.69 mmol, 74%) as a colorless oil: IR (film): 2956, 1611, 1256 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, J=7.0 Hz, 3H), 2.08 (dddd, J=16.9, 6.9, 4.3, 1.5 Hz, 1H), 2.17 (s, 3H), 2.39–2.49 (m, 1H), 2.28 (sextet, J=7.0 Hz, 1H), 3.83 (s, 3H), 5.79 (dt, J=9.2, 4.3 Hz, 1H), 6.35 (dt, J=9.2, 1.7 Hz, 1H), 6.66 (s, 1H), 6.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 20.3, 31.2, 32.1, 55.5, 108.6, 124.0, 124.2, 126.0, 126.8, 128.7, 139.4, 156.9; MS m/z (%): 188 (M^+, 57), 173 (100). Anal. calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found C, 82.97; H, 8.28.

3.1.2. 1-Dimethoxymethyl-5-methoxy-3,6-dimethyl-indan (4). To a stirred solution of **5** (0.546 g, 2.90 mmol) in TMOF (15 mL), was added TTN·$3H_2O$ (1.42 g, 3.20 mmol) at 0°C, which promptly dissolved. The mixture was stirred for 1 min at 0°C and an abundant precipitation was observed. The resulting suspension was filtered through a silica gel pad (200–400 mesh, ca. 10 cm), using CH_2Cl_2 as eluent. The filtrate was washed with H_2O (twice), with brine, and dried over anhydrous $MgSO_4$. The solvent was concentrated under reduced pressure giving a yellow oil. The residue was purified by flash chromatography (silica gel 200–400 mesh, eluent: hexanes (80%), CH_2Cl_2 (10%) and EtOAc (10%)) immediately after concentration of the solvent, affording **4** (0.660 g, 2.64 mmol, 91%) as a colorless oil: IR (film): 2953, 2830, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J=6.9 Hz, 3H), 1.76 (ddd, J=13.0, 8.5, 6.7 Hz, 1H), 2.19 (s, 3H), 2.22–2.31 (m, 2H), 3.18–3.27 (m, 1H), 3.35 (s, 3H), 3.40 (s, 3H), 3.35–3.40 (m, 1H), 3.81 (s, 3H), 4.23 (d, J=7.3 Hz, 1H), 6.65 (s, 1H), 7.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 20.9, 36.8, 38.1, 45.6, 53.1, 54.5, 55.4, 105.1, 107.5, 124.6, 127.6, 133.6, 148.2, 157.5; MS m/z (%): 250 (M^+, 9), 75 (100). Anal. calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found C, 71.85; H, 8.60.

3.1.3. 3,6-Dimethyl-5-methoxy-indan-1-carbaldehyde (13a). To a stirred solution of the acetal **4** (0.0558 g, 0.223 mmol) in glacial acetic acid (0.7 mL), was added H_2O (2 drops). The mixture was heated at a controlled range of temperature (75–80°C) for 40 min. The resulting solution was diluted with Et_2O and a saturated solution of $NaHCO_3$ was added dropwise until pH 7. The organic phase was washed with saturated aqueous solution of $NaHCO_3$ (twice), with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, giving **13a** (0.0391 g, 0.192 mmol, 86%) as a yellow oil: IR (film): 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, J=7.3 Hz, 3H), 1.86 (ddd, J=13.2, 8.5, 7.3 Hz, 1H), 2.20 (s, 3H), 2.66 (ddd, J=13.2, 7.8, 3.8 Hz, 1H), 3.25–3.34 (m, 1H), 3.80–3.86 (m, 1H), 3.83 (s, 3H), 6.71 (s, 1H), 7.04 (s, 1H), 9.58 (d, J=2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 20.8, 35.1, 38.7, 55.5, 56.2, 105.8, 125.6, 126.8, 129.0, 148.3, 158.3, 200.6; MS m/z (%): 204 (M^+, 11), 175 (100); HRMS calc. for $C_{13}H_{16}O_2$ 204.1150. Found 204.1149.

3.1.4. 3,6-Dimethyl-5-methoxy-1-(2-methyl-propenyl)-indan (14). To a stirred solution of $Ph_3CH(CH_3)_2Br$ [22] (0.151 g, 0.392 mmol) in anhydrous THF (3 mL) under nitrogen, was added dropwise n-BuLi (2.09 M in hexanes, 0.18 mL, 0.38 mmol) at 10°C. The resulting red solution was stirred for 20 min at 10°C. Then, a solution of the aldehyde **13a** (0.0786 g, 0.385 mmol) in anhydrous THF (2 mL) was added dropwise. The mixture was stirred for 30 min at 10°C. The reaction was quenched with H_2O (3 mL) and extracted with Et_2O (three times). The organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, giving a yellow solid. This solid was purified by flash chromatography (silica gel 200–400 mesh, eluent: hexanes (80%), CH_2Cl_2 (10%) and EtOAc (10%)) affording impure starting material (0.0081 g) and **14** (0.0562 g, 0.244 mmol, 63%) as a colorless oil: IR (film): 1614, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J=7.0 Hz, 3H), 1.74 (d, J=1.3 Hz, 3H), 1.78 (d, J=1.3 Hz, 3H), 1.87–2.02 (m, 2H), 2.18 (s, 3H), 3.18–3.29 (m, 1H), 3.81 (s, 3H), 3.95–4.03 (m, 1H), 5.10–5.14 (m, 1H), 6.67 (s, 1H), 6.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 18.1, 21.0, 25.8, 38.5, 41.6, 42.5, 55.6, 105.6, 124.9, 126.2, 128.8, 131.1, 138.0, 147.2, 157.1; MS m/z (%): 230 (M^+, 40), 215 (100); HRMS calc. for $C_{16}H_{22}O$: 230.1671. Found 230.1667.

3.1.5. (±)-Mutisianthol (3). Under nitrogen, NaH (0.328 g, 8.20 mmol, 60% in mineral oil) was washed with anhydrous hexanes (twice). After a few minutes under nitrogen, anhydrous DMF (5 mL) was added. To this mixture was slowly added a solution of EtSH (0.40 mL, 5.5 mmol) in anhydrous DMF (0.4 mL) at 0°C and the resulting yellow-gray solution was stirred for 20 min at room temperature. A solution of **14** (0.0419 g, 0.182 mmol) in DMF (1 mL) was then added dropwise and the resulting mixture was stirred for 5 h at 140°C, becoming slightly brown. The mixture was cooled to the room temperature and a saturated solution of NH_4Cl (5 mL) was added. The mixture was extracted with Et_2O (3 times) and the organic phase was washed with water, with brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resulting brown oil was purified by flash chromatography (30% AcOEt in hexanes) giving starting material (0.0078 g, 0.034 mmol, 19%) and **14** (0.0285 g, 0.132 mmol, 72%) as a white solid: mp: 82.1–83.0°C; IR (film): 3371, 1619, 1259, 813 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J=7.0 Hz, 3H), 1.74 (d, J=1.3 Hz, 3H), 1.77 (d, J=1.3 Hz, 3H), 1.88–1.97 (m, 2H), 2.21 (s, 3H), 3.14–3.25 (m, 1H), 3.95–3.99 (m, 1H), 5.10–5.13 (m, 1H), 6.61 (s, 1H), 6.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 18.1, 20.9, 25.8, 38.1, 41.5, 42.4, 110.1, 121.6, 126.3, 128.6, 131.2, 138.7, 147.9, 152.8; MS m/z (%): 216 (M^+, 42), 187 (100).

Acknowledgements

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