Pergamon

Tetrahedron Letters 42 (2001) 1155–1157

TETRAHEDRON LETTERS

Enantioselective synthesis of a *trans*-ethenyl-hydrindene, a useful steroid CD-ring diene precursor

Marcello Di Filippo, Irene Izzo, Alessandro Vece, Francesco De Riccardis* and Guido Sodano

Dipartimento di Chimica, Università di Salerno, Via S. Allende, Baronissi, I-84081 Salerno, Italy

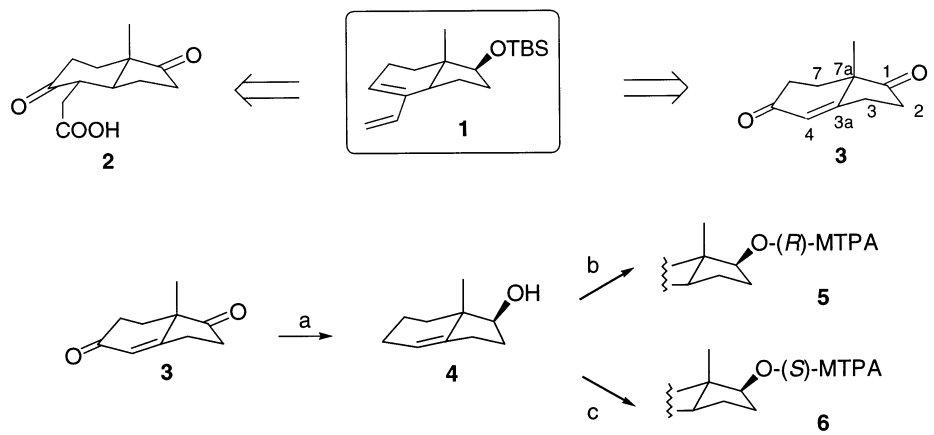
Received 23 November 2000; accepted 29 November 2000

Abstract—A highly efficient enantioselective synthesis of protected *trans*-hydrindenol diene **1** is described starting from the readily available Hajos–Parrish ketone. The reported methodology represents the most convenient route (10 steps, 31% overall yield) to both enantiomeric forms of a steroid (estrogenic) CD-ring diene precursor. © 2001 Published by Elsevier Science Ltd.

In recent years many strategies have been reported for the synthesis of steroids and their analogs using cycloaddition reactions.[1] However, only a few of the proposed procedures are based on the convergent coupling of an upper CD bicyclic fragment to a ring A precursor.[2] A recent example of this approach has been reported by Rigby and co-workers for the synthesis of enantiomerically pure (+)-estradiol.[3] The synthetic procedure is based on a chromium(0)-promoted benzannulation reaction in which the diene partner **1** was prepared in 26% overall yield (eight steps) from the rare indandione precursor **2**, available only through microbial degradation of soya sterols.[4]

In this communication we wish to report an alternative, high yielding, synthesis of **1** starting from the readily available optically pure hydrindenedione **3** and based on chemistry developed by our own group for the preparation of similar dienes used for the synthesis of steroid analogs.[2b,c]

Construction of the steroid CD-ring precursor started with the enantioselective synthesis of hydrindenedione (+)-**3**, with an excellent e.e. ($\geq$99%),[5] following the Hajos–Parrish procedure.[6] Deoxygenation and stereoselective reduction at C-1 with $NaBH_4$/CF_3COOH in acetonitrile, following a protocol out-



Scheme 1. (a) 3.5 equiv. of $NaBH_4$, 16 equiv. of CF_3COOH, CH_3CN, –20°C, 3.5 h, 80%; (b) 2 equiv. of (*S*)-(+)-MTPA-Cl, pyridine; (c) 2 equiv. of (*R*)-(–)-MTPA-Cl, pyridine.

Keywords: steroids; asymmetric synthesis; dienes; Stille reaction.

* Corresponding author.

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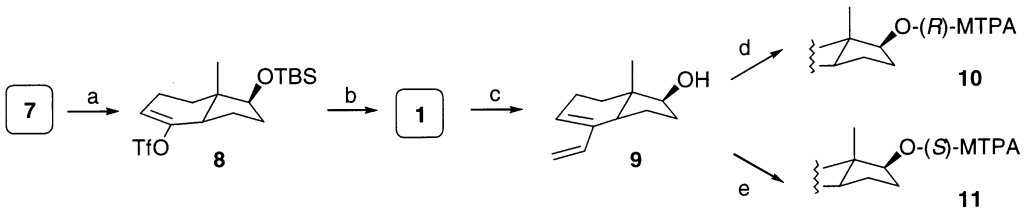
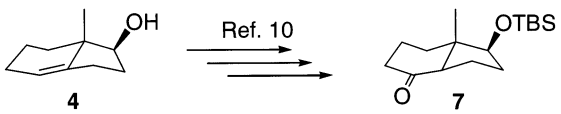
PII: S0040-4039(00)02193-6



Scheme 2. (a) 2.5 equiv. of $LiN(SiMe_3)_3$, THF, −78°C, 1 h then 2.5 equiv. of $PhN(SO_2CF_3)_2$, −78°C, 0.3 h, then 0.5 h at rt; (b) 1.2 equiv. of CH_2=CH–Sn-*n*Bu_3, 4.5 equiv. of LiCl, 0.03 equiv. of $(PPh_3)_4Pd$, THF, reflux, 3 h (82%, two steps); (c) 10 equiv. of TBAF, THF, 3 h, 96%; (d) 2 equiv. of (*S*)-(+)-MPTA-Cl, pyridine; (e) 2 equiv. of (*R*)-(−)-MTPA-Cl, pyridine.

lined by Gribble (Scheme 1),[7] produced, in a single step and 80% yield, the (+)-(1*S*,7a*S*)-2,3,5,6,7,7a-hexahydro-7a-methyl-1*H*-inden-1-ol **4**. The enantiomeric purity of this intermediate and, indirectly, that of its precursor **3**,[8] was confirmed through the Mosher's ester method.[9] Thus, derivatization of the C-1 alcohol group of **4** with (+)- and (−)-α-methoxy-α-[(trifluoromethyl)-phenylacetyl]chlorides [(+)- and (−)-MTPA-Cl] quantitatively furnished the diastereomeric derivatives **5** and **6**. Evaluation of the ^{1}H NMR resonances of the deshielded C-1 protons (**5**: $\delta = 4.85$, 1H, dd, $J = 8.9$, 8.7 Hz; **6**: $\delta = 4.79$, 1H, dd, $J = 8.7$, 8.5 Hz) confirmed the enantiomeric excess determined on **3** by optical rotation ($\geq 99\%$; in both derivatives only one diastereoisomer was detected in the 400 MHz ^{1}H NMR spectrum).

Hydrindenol **4** was then transformed into the *trans*-hydrindane derivative **7** in a seven step sequence and in 48% overall yield as previously reported by Mouriño and co-workers.[10]



With **7** in our hands the construction of diene **1** was achieved by a route based on our own earlier experience with the palladium-mediated vinylation reaction[2b,c] (Scheme 2). Ketone **7** was thus kinetically enolized with lithium bis(trimethylsilyl)amide and the enolate trapped with *N*-phenyltrifluoromethanesulfonimide[11] to afford the stable enoltriflate **8**.[12] Stille palladium-catalyzed coupling[13] between **8** and vinyltributyltin, in the presence of tetrakis(triphenylphosphine)palladium(0) and lithium chloride, in refluxing THF, gave the expected conjugated diene (+)-(1*S*, 3a*S*,7a*S*)-4-ethenyl-1-[(*tert*-butyldimethylsilyl)oxy]-2,3, 3a,6,7,7a-hexahydro-7a-methyl-1*H*-4-indene **1** in 82% overall yield from **7**.

The specific rotation value of **1**—$[\alpha]_D$ +5.7 ($c = 1.0$, $CHCl_3$)—was unexpectedly very different from that reported by Rigby[3]—$[\alpha]_D$ +36.1 ($c = 1.0$, $CHCl_3$)—in contrast with the fact that all the reactions from **3** to **1** should not induce racemization. In this case we determined the enantiomeric purity of target **1** by the Mosher esters method[9] applying it to the desilylated diene **9**[14] (Scheme 2). In the ^{1}H NMR spectra of the diastereomeric esters **10** and **11** only one isomer was detected again confirming an enantiomeric purity $\geq 99\%$ and, consequently, the correctness of the optical rotation value found for **1**.[15]

In conclusion, we have synthesized the enantiomerically pure diene **1** in 10 steps and in 31% overall yield from the readily available hydrindenedione (+)-**3**. It is interesting to note that since the enantiomer of **3** could be readily prepared, this route provides access also to the unnatural (−)-estradiol and other enantiomeric steroids.

Acknowledgements

This work has been supported by the MURST (PRIN 'Chimica dei Composti Organici di Interesse Biologico').

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It should be noted that an enantiomerically pure hydrated precursor of **3**, the (3a*S*,7a*S*)-(+)-hexahydro-3a-hydroxy-7a-methyl-1,5-indanedione, is also available from the Aldrich Chemicals Co., Milwaukee, USA.

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12. Compound **8**: $[\alpha]=+13.1$ ($c=1.0$, $CHCl_3$); HREIMS, m/z: 414.1500 (calcd for $C_{17}H_{29}F_3O_4SSi$, 414.1508); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.57 (1H, dd, $J=6.9$, 3.5 Hz, H-5), 3.73 (1H, dd, $J=9.1$, 7.0 Hz, H-1), 2.40–1.20 (9H), 0.88 (9H, s, -SiC$(CH_3)_3$), 0.80 (3H, s, CH_3), 0.02 (6H, s, -Si$(CH_3)_2$; ^{13}C NMR ($CDCl_3$, 100 MHz): 149.7, 118.6 (q, $J=340$ Hz), 116.3, 79.4, 46.3, 44.6, 32.3, 31.0, 25.7 (×3), 23.5, 21.1, 18.0, 11.0, −4.5, −4.8.
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14. Compound **9**: $[\alpha]=+4.1$ ($c=1.0$, $CHCl_3$); HREIMS, m/z: 178.1349 (calcd for $C_{12}H_{18}O$, 178.1358); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.21 (1H, dd, $J=17.7$, 11.3 Hz, -CH=), 5.67 (1H, bs, H-5), 5.17 (1H, bd, $J=17.7$ Hz, C*H*H=), 4.86 (1H, bd, $J=11.3$ Hz, CH*H*=), 3.77 (1H, dd, $J=8.6$, 7.7 Hz, H-1), 2.30–0.90 (10H), 0.71 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 138.5, 137.6, 126.5, 111.7, 80.1, 44.3, 43.3, 32.9, 30.9, 24.3, 23.6, 10.6.
15. An explanation to justify the different values of specific rotation for **1** may reside in the fact that this diene is relatively unstable, leading to decomposition products when stored even at −20°C for more than 2–3 weeks. We measured the optical rotation immediately after its synthesis and we have found the same value after two different preparations.