Stereoselective Total Synthesis of a Novel D-Homosteroid by a Twofold Heck Reaction

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Dedicated to Professor Günter Helmchen on the occasion of his 60th birthday

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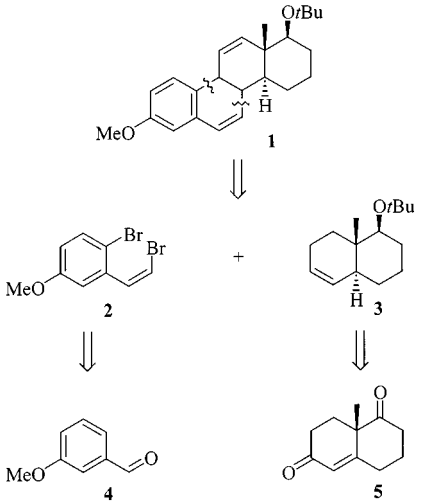
The D-homosteroid **1** was synthesized by two successive Heck reactions starting from enantiopure **3** and the bromoarene **2** containing a (*Z*)-bromovinyl group. The first intermolecular Pd-catalyzed reaction leads to **6** in a highly regio- and diastereoselective way which forms **1** with an unusual *cis*-junction of the rings B and C by a second intramolecular Heck reaction.

Introduction

Among other ring-enlarged or -contracted steroidal systems D-homosteroids are of special pharmacological and synthetical interest.[1] Several methods have been developed to obtain D-homosteroids from normal steroids, which mainly involve rather unselective ring enlargement reactions by rearrangement.[2] Alternatively D-homoestrone derivatives have been obtained from natural estrone with high stereoselectivity employing a domino Knoevenagel hetero Diels–Alder process.[3] However, a general total or partial total synthetic approach not relying on natural precursors appears to be more promising with regard to a greater structural versatility of the products. In this context especially, the Heck reaction[4] has proven to be a versatile procedure to obtain carbo- and heterocyclic systems in the synthesis of complex natural products.

In this paper we describe the formation of the novel D-homoestradiol derivative **1** using our strategy to form the B-ring of the steroid frame by a double Heck reaction. This approach has already been successfully employed in the synthesis of estrone.[5] Double inter-/intramolecular Heck reactions have also been used in the preparation of novel aza-heterocycles.[6] The retrosynthetic analysis of **1** leads to (*Z*)-(2-bromoethenyl)-4-methoxy-bromobenzene **(2)** and the octahydronaphthalene derivative **3** (Scheme 1). The latter compound can easily be obtained from the Wieland–Miescher ketone **5**[7] in a five-step sequence introduced by Tsuji et al. which includes a stereoselective intramolecular Pd-catalyzed rearrangement of an allyl formate to give the desired *trans*-annulation of the two rings.[8] The doubly functionalized arene **2** was prepared from the commercially available aldehyde **4** in three steps by bromination, Corey–Fuchs reaction with tetrabromomethane,[9] and selective removal of a bromine atom.[10]



Scheme 1. Retrosynthetic analysis of D-homoestradiol **1**

Results and Discussion

In the Heck reaction of **2** and **3** we expected a selective coupling of the vinyl moiety since we had previously shown that vinyl bromides are more reactive than bromoarenes in Pd^0-catalyzed reactions.[5] The facial selectivity of this reaction should be controlled by the angular methyl group directing the attack to the α-side *anti* to the methyl group in **3**. This is indeed the case. The reaction of **2** and **3** at 70 °C in the presence of a catalytic amount of $Pd(OAc)_2$ and triphenylphosphane, tetrabutylammonium acetate and a small amount of water led to **6** in 52% yield (Scheme 2). In addition, the butadiene **7** was obtained in 5–10% yield. The addition of water is quite important, since it leads to a significant increase in the reaction rate. To suppress the formation of **7**, which is formed by a Pd-catalyzed autocoupling of the vinyl bromide **2**, a twofold excess of **3** was used. Compound **3** is stable under these reaction conditions and

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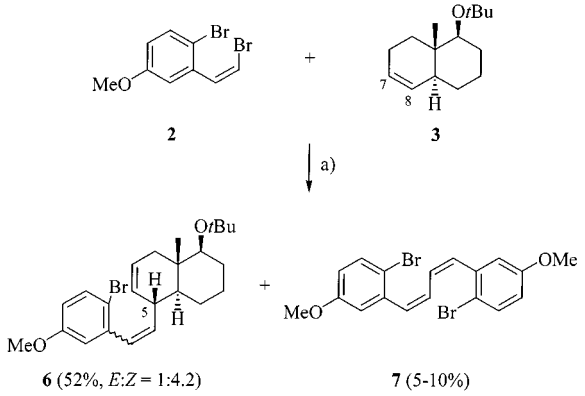
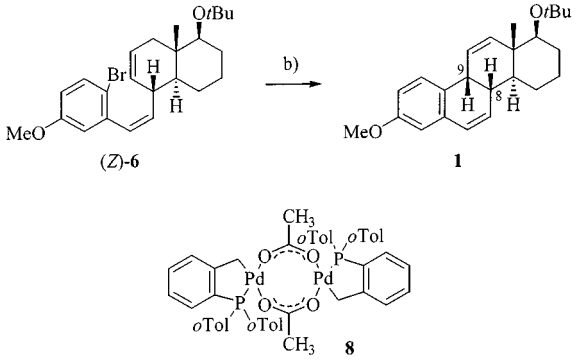
can be reisolated quantitatively. Compound **6** is obtained as a 4.2:1 mixture of the desired (*Z*)- and the unwanted (*E*)-isomer, which could easily be separated by chromatography on $AgNO_3$-doped silica gel. The formation of (*E*)-**6** can be explained by a readdition and elimination of the intermediately formed H−Pd−Br species at the styrene moiety in **6**. It is somewhat surprising that a double bond shift does not take place either here or at the second alkene group, as this is a usual side reaction in Heck reactions. The (*Z*)/(*E*)-isomerization could be suppressed by the addition of a silver salt; however, this leads to an overall decrease in the yield. The selective attack at C-8 of **3** in the reaction with **2** needs some explanation. Usually, the C−C-coupling takes place at the less-hindered carbon of the alkene moiety. In **3** C-7 should be less hindered than C-8; we therefore assume that the reaction is governed by a stereoelectronic control. It is generally accepted that an alkene inserts into the initially formed σ-alkenyl palladium(II) complex via an unsymmetrical four-center transition state. If one accepts that in the transition state the alkene−Pd bond is formed to a higher extent than the C−C-bond, an attack of Pd at C-7 in **3** would lead to a chair-like transition state with the formation of (*Z*)-**6**. In contrast, an attack of Pd at C-8 in **3** would give an energetically less-favored boat-like transition state.



Scheme 2. Intermolecular Heck reaction of **2** and **3**: a) 10 mol-% $Pd(OAc)_2$, 25 mol-% PPh_3, 2.5 equiv. nBu_4NOAc, **2**:**3** = 1:2, DMF/CH_3CN/H_2O (5:5:1), 70 °C, 11 h

For the next step, the intramolecular Heck reaction of (*Z*)-**6** to give **1**, several catalysts were investigated (Scheme 3). The usual Pd^0 complexes with triphenylphosphane as ligand were not suitable. However, in the presence of the palladacycle **8** introduced by Herrmann and Beller et al.[11] compound **1** could be obtained as a single diastereomer in 74% yield. The coupling was performed at 115 °C with tetrabutylammonium acetate as base; again a small amount of water was added which greatly increased the reaction rate. Compound **1** represents a new type of steroid skeleton with an unnatural *cis*-annulation of rings B and C. This type of compound has received little attention so far, since there was no synthetic access available.

We also tried to synthesize steroids with a *cis*-*cis* annulation of the rings BC and CD. For this purpose we prepared the *cis*-fused indene derivative **9** (Figure 1).[8] However, reaction of **9** with the bromoarene derivative **2** under a



Scheme 3. Intramolecular Heck reaction of (*Z*)-**6**: b) 2.0 mol-% **8**, 2.5 equiv. nBu_4NOAc, DMF/CH_3CN/H_2O (5:5:1), 115 °C, 15 h, 74%

variety of conditions led only to the butadiene **7**; the indene derivative **9** is stable under the reaction conditions and could be reisolated almost quantitatively. A probable explanation for the lack of reactivity of **9** could be its folded conformation, which was confirmed by MM2 calculations. Thus, neither an attack at the double bond from the β-face due to the shielding of the angular methyl group nor from the α-face due to an interaction with the cyclopentene moiety is possible.

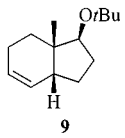


Figure 1. *cis*-fused indene derivative **9**

Structure Determination of 1

The configuration at C-8 and C-9 in **1** was confirmed by ^1H-^1H-NOESY experiments. Characteristic signals in the ^1H NMR spectrum of **1** are the singlets at δ = 0.95 for the angular methyl group, the singlet at δ = 1.14 for the O*t*Bu group, the doublet of doublets for 18-H with *J* = 11.0 and 4.4 Hz as well as the singlet for the OCH_3 group at δ = 3.79. The hydrogens at the two olefinic double bonds resonate at δ = 5.98 as a doublet of doublets with *J* = 9.8 and 6.6 Hz (7-H), at δ = 6.10 as a multiplet (11-H, 12-H) and at δ = 6.38 as a doublet with *J* = 9.8 Hz (6-H). The signal for 8-H is found at δ = 2.47 as a doublet of triplets with *J* = 10.9 and 6.6 Hz and that for 9-H at δ = 3.50 as a doublet with *J* = 6.6 Hz. This clearly indicates that 8-H holds an axial orientation with an antiperiplanar arrangement to 14-H and a synclinal orientation to 9-H.

Conclusion

The novel D-homoestradiol derivative **1** was synthesized stereoselectively in a highly efficient approach by forming the ring B using two subsequent Heck reactions. Rings B and C of **1** have an unnatural *cis*-configuration and the two double bonds in the 6,7 and 11,12 positions provide the opportunity for further derivatisation.[5b] By variation of

both building blocks **2** and **3** a large number of new steroid analogues should be accessible using this procedure.

Experimental Section

General: All reactions were performed in oven-dried glassware under an argon atmosphere. Solvents were degassed by the freeze-pump-thaw methodology. TLC chromatography was performed on precoated silica gel SIL G/UV$_{254}$ plates (Macherey, Nagel Co.), and silica gel 32−63 (0.032−0.064 mm) (Macherey, Nagel Co.) was used for column chromatography. Melting points: Mettler FP61. Optical rotations: Perkin−Elmer 241. IR: Bruker IFS 25. UV/Vis: Perkin−Elmer Lambda 9. NMR: Varian VXR-200 (200 MHz, ^{1}H), Bruker AM-300 (300 MHz, 75 MHz, ^{1}H and ^{13}C, respectively), Varian VXR-500 (500 MHz, 125 MHz, for ^{1}H and ^{13}C, respectively). For ^{1}H and ^{13}C NMR, $CDCl_3$ as solvent, TMS as internal standard. Chemical shifts are reported on the δ scale. Signals are quoted as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br (broad). MS: Varian MAT 311A (70 eV, EI). HRMS: Varian MAT 731. Elemental analysis: Mikroanalytisches Labor des Instituts für Organische Chemie der Universität Göttingen.

Intermolecular Heck Reaction of 2 and 3: A solution of the octahydronaphthalene **3** (445 mg, 2.00 mmol), the bromoarene **2** (292 mg, 1.00 mmol) and nBu$_4$NOAc (905 mg, 3.00 mmol) in DMF/CH_3CN/H_2O (1:1:0.2, 15 mL) was thoroughly degassed and warmed to 40 °C. Triphenylphosphane (65.5 mg, 25 mol-%) and $Pd(OAc)_2$ (22.5 mg, 10 mol-%) were added subsequently under argon. The reaction mixture was heated to 70 °C and stirred for 11 h. After cooling to room temp., diethyl ether (25 mL) and water (25 mL) were added, the layers were separated and the aqueous phase extracted with diethyl ether (2 × 15 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give the desired product (*Z*)-**6** (182 mg, 0.42 mmol, 42%), its isomer (*E*)-**6** (43.3 mg, 0.10 mmol, 10%), and the dimer **7** (21.2 mg, 0.05 mmol, 10%) after twofold column chromatography (petroleum ether/ethyl acetate 250:1 on SiO_2 and petroleum ether/ethyl acetate 40:1 on $AgNO_3$-doped silica gel). Furthermore 266 mg (1.20 mmol) of the remnant octahydronaphthalene **3** were reisolated.

(−)-(1*R*,4a*S*,5*R*,8a*S*)-5-(*Z*)-[2-(2-Bromo-5-methoxyphenyl)vinyl]-1-*tert*-butoxy-8a-methyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene [(*Z*)-6]: R_f = 0.07 (petroleum ether), 0.34 ($AgNO_3$-doped SiO_2, petroleum ether/ethyl acetate, 40:1). − $[\alpha]_D^{20}$ = −61.7 (c = 0.3, $CHCl_3$). − UV (CH_3CN): λ_{max} (lg ε) = 202 nm (3.75), 291 (2.95). − IR (KBr) $\tilde{\nu}$ = 3056, 3012, 2974, 2930, 2870, 1654, 1592, 1466, 1362, 808, 688 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75 (s, 3 H, 8a-CH_3), 0.79−1.05 (m, 2 H, 3-H_2), 1.15 (s, 9 H, 1-O*t*Bu), 1.18−1.70 (m, 5 H, 2-H_2, 4-H_2, 4a-H), 1.77 (d_{br}, J = 17.3 Hz, 1 H, 8-H_a), 2.10 (dd_{br}, J = 17.3, 5.2 Hz, 1 H, 8-H_b), 2.80 (m_c, 1 H, 5-H), 3.02 (dd, J = 11.2, 3.5 Hz, 1 H, 1-H), 3.76 (s, 3 H, 7′-OCH_3), 5.40 (m_c, 1 H, 7-H), 5.44 (dd, J = 11.3, 11.3 Hz, 1 H, 1′-H), 5.68 (dddd, J = 9.8, 5.3, 1.9, 1.9 Hz, 1 H, 6-H), 6.45 (d, J = 11.3 Hz, 1 H, 2′-H), 6.66 (dd, J = 9.1, 3.0 Hz, 1 H, 6′-H), 6.78 (d, J = 3.0 Hz, 1 H, 8′-H), 7.42 (d, J = 9.1 Hz, 1 H, 5′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 11.4 (8a-CH_3), 24.2 (C-3), 25.8 (C-4), 29.2 [OC(CH_3)$_3$], 30.8 (C-2), 37.6 (C-8a), 38.6 (C-5), 39.0 (C-8), 45.8 (C-4a), 55.4 (7′-OCH_3), 72.7 [OC(CH_3)$_3$], 78.4 (C-1), 114.1 (C-6′), 114.4 (C-4′), 115.9 (C-8′), 127.0 (C-6), 127.7 (C-7), 129.5 (C-2′), 132.9 (C-5′), 137.2 (C-1′), 138.4 (C-3′), 158.3 (C-7′). − EI-MS (70 eV): m/z (%) = 434.2 (100) [M^+], 378.1 (14) [$M^+ - C_4H_8$], 359.1 (16) [$M^+ - C_4H_8 - H_2O$], 353.3 (29) [M^+ − Br], 297.2 (30) [$M^+ - C_4H_8$ − Br], 288.0 (57) [$C_{15}H_{13}BrO^+$], 279.2 (61) [$M^+ - C_4H_8 - H_2O$ − Br], 209.1 (89) [$C_{15}H_{13}O^+$], 146.1 (40) [$C_{11}H_{14}^+$], 57.0 (83) [$C_4H_9^+$]. − EI-HRMS ($C_{24}H_{33}O_2Br$): calcd. 432.1664; found: 432.1664.

(−)-(1*R*,4a*S*,5*R*,8a*S*)-5-(*E*)-[2-(2-Bromo-5-methoxyphenyl)vinyl]-1-*tert*-butoxy-8a-methyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene [(*E*)-6]: R_f = 0.11 (petroleum ether), 0.25 ($AgNO_3$-doped SiO_2, petroleum ether/ethyl acetate, 40:1). − $[\alpha]_D^{20}$ = −55.0 (c = 0.2, $CHCl_3$). − UV (CH_3CN): λ_{max} (lg ε) = 220 nm (3.77), 254 (3.57), 305 (2.87). − IR (KBr): $\tilde{\nu}$ = 3022, 2972, 2930, 2852, 1644, 1594, 1464, 1360, 968, 806, 700 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (s, 3 H, 8a-CH_3), 1.18 (s, 9 H, 1-O*t*Bu), 1.03−1.13 (m, 1 H, 3-H_a), 1.19−1.28 (m, 2 H, 3-H_b, 4a-H), 1.45−1.73 (m, 4 H, 2-H_2, 4-H_2), 1.81 (m, 1 H, 8-H_a), 2.16 (dd_{br}, J = 17.5, 5.7 Hz, 1 H, 8-H_b), 2.62 (m_c, 1 H, 5-H), 3.07 (dd, J = 11.3, 3.8 Hz, 1 H, 1-H), 3.80 (s, 3 H, 7′-OCH_3), 5.46 (d_{br}, J = 10.1 Hz, 1 H, 7-H), 5.71 (dddd, J = 10.1, 5.7, 2.2, 2.2 Hz, 1 H, 6-H), 5.92 (dd, J = 15.6, 9.3 Hz, 1 H, 1′-H), 6.66 (dd, J = 8.7, 3.0 Hz, 1 H, 6′-H), 6.68 (d, J = 15.6 Hz, 1 H, 2′-H), 7.02 (d, J = 3.0 Hz, 1 H, 8′-H), 7.41 (d, J = 8.7 Hz, 1 H, 5′-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.3 (8a-CH_3), 24.1 (C-3), 25.7 (C-4), 29.3 [OC(CH_3)$_3$], 30.9 (C-2), 37.9 (C-8a), 39.1 (C-8), 44.0 (C-5), 45.4 (C-4a), 55.5 (7′-OCH_3), 72.7 [OC(CH_3)$_3$], 78.5 (C-1), 112.0 (C-8′), 114.1 (C-4′), 114.5 (C-6′), 126.6 (C-6), 128.3 (C-7), 129.7 (C-2′), 133.4 (C-5′), 137.3 (C-1′), 138.2 (C-3′), 158.9 (C-7′). − EI-MS (70 eV): m/z (%) = 434.2 (74) [M^+], 377.1 (9) [$M^+ - C_4H_9$], 359.1 (17) [$M^+ - C_4H_9 - H_2O$], 279.2 (40) [$M^+ - C_4H_9 - H_2O$ − Br], 199.0 (18) [MeOPh(Br)CH^+], 171.1 (19) [$C_{12}H_{11}O^+$], 145.1 (68) [$C_{11}H_{13}^+$], 105.1 (13) [$C_8H_9^+$], 57.0 (100) [$C_4H_9^+$], 41.1 (26) [$C_3H_5^+$]. − EI-HRMS ($C_{24}H_{33}O_2Br$): calcd. 432.1664, found: 432.1664.

1,4-Bis(2-bromo-5-methoxyphenyl)-1,3-butadiene (7): R_f = 0.13 (petroleum ether/ethyl acetate, 100:1), m.p. 167−168 °C. − UV (CH_3CN): λ_{max} (lg ε) = 223 nm (3.77), 334 (3.83), 344 (3.82). − IR (KBr): $\tilde{\nu}$ = 3042, 2832, 1588, 1564, 1464, 816, 644 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 6.71 (dd, J = 8.7, 3.1 Hz, 1 H, 4′-H), 7.00 (m_c, 2 H, 1-H, 2-H), 7.16 (d, J = 3.1 Hz, 1 H, 6′-H), 7.45 (d, J = 8.7 Hz, 1 H, 3′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 55.5 (OCH_3), 111.2 (C-6′), 114.8 (C-2′), 115.6 (C-4′), 131.5, 132.4, 133.6 (C-1, C-2, C-3′), 137.3 (C-1′), 159.0 (C-5′). − EI-MS (70 eV): m/z (%) = 424.2 (29) [M^+], 343.2 (16) [M^+ − Br], 264.2 (100) [M^+ − Br − Br]. − $C_{18}H_{16}Br_2O_2$ (424.1): calcd. C 50.97, H 3.80; found C 51.21, H 3.98.

Intramolecular Heck Reaction of (*Z*)-6. (−)-18β-*tert*-Butoxy-3-methoxy-9β-D-homo-estrane-1,3,5,(10),6,11-pentaene (1): A thoroughly degassed solution of *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) (**8**; 3.4 mg, 2.0 mol-%), (*Z*)-**6** (64.0 mg, 0.15 mmol) and nBu$_4$NOAc (111 mg, 0.37 mmol) in DMF/CH_3CN/H_2O (1:1:0.2, 5 mL) was stirred for 15 h at 115 °C. After cooling the reaction mixture to room temp., water (15 mL) and diethyl ether (15 mL) were added and the aqueous phase was extracted with diethyl ether (2 × 25 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum ether/ethyl acetate, 100:1) gave **1** (39.1 mg, 0.11 mmol, 74%): R_f = 0.11 (petroleum ether/ethyl acetate, 100:1). − $[\alpha]_D^{20}$ = −75.0 (c = 0.3, $CHCl_3$). − UV (CH_3CN): λ_{max} (lg ε) = 229 nm (3.85), 274 (3.15), 301 (3.06), 312 (3.03), 352 (2.24). − IR (neat): $\tilde{\nu}$ = 3026, 2972, 2930, 2862, 1626, 1572, 1464, 1362, 818, 686 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (s, 3 H, 13-CH_3), 1.14 (s, 9 H, 18-O*t*Bu), 1.17−1.32 (m, 2 H, 16-H_2), 1.44−1.54 (m, 3 H, 14-H, 17-H_2), 1.57−1.67 (m, 2 H, 15-H_2), 2.47 (ddd, J = 10.9, 6.6,

6.6 Hz, 1 H, 8-H), 3.01 (dd, J = 11.0, 4.4 Hz, 1 H, 18-H), 3.50 (d, J = 6.6 Hz, 1 H, 9-H), 3.79 (s, 3 H, 3-OCH_3), 5.98 (dd, J = 9.8, 6.6 Hz, 1 H, 7-H), 6.10 (m, 2 H, 11-H, 12-H), 6.38 (d, J = 9.8 Hz, 1 H, 6-H), 6.58 (d, J = 2.7 Hz, 1 H, 4-H), 6.71 (dd, J = 8.3, 2.7 Hz, 1 H, 2-H), 7.15 (d, J = 8.3 Hz, 1 H, 1-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.4 (13-CH_3), 22.8 (C-16), 24.4 (C-15), 29.0 [18-OC(CH_3)$_3$], 30.3 (C-17), 33.3 (C-8), 36.6 (C-9), 40.7 (C-14), 41.4 (C-13), 55.2 (3-OCH_3), 73.1 [18-OC(CH_3)$_3$], 75.2 (C-18), 111.8 (C-4), 111.9 (C-2), 123.0 (C-11), 126.8 (C-6), 127.5 (C-1), 130.2 (C-10), 132.4 (C-7), 134.1 (C-5), 137.3 (C-12), 157.9 (C-3). − EI-MS (70 eV): m/z (%) = 352.3 (54) [M^+], 295.2 (21) [$M^+ - C_4H_9$], 277.2 (100) [$M^+ - C_4H_9 - H_2O$], 171.1 (54) [$C_{12}H_{11}O^+$], 158.1 (21) [$C_{11}H_{10}O^+$], 91.1 (14) [$C_7H_7^+$], 57.1 (77) [$C_4H_9^+$], 41.0 (29) [$C_3H_5^+$]. − EI-HRMS ($C_{24}H_{32}O_2$): calcd. 352.2402, found: 352.2402.

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