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Highly Efficient, Enantioselective Synthesis of (+)-Grandisol from a C_2-Symmetric Bis(α,β-butenolide)

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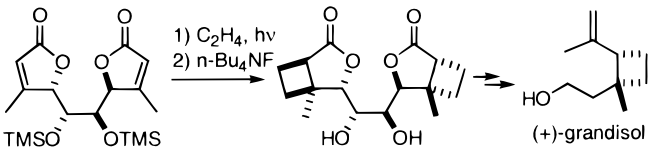
ABSTRACT

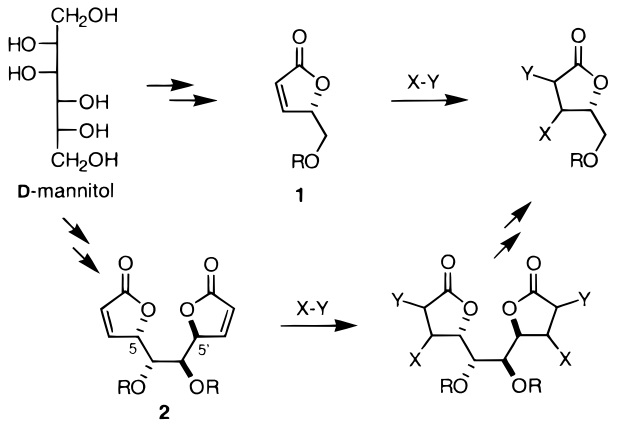


A new, very efficient, enantioselective synthesis of the sexual attracting insect pheromone (+)-grandisol has been developed, in which the key step is the double [2 + 2] photocycloaddition of ethylene to a bis(α,β-butenolide) readily available from D-mannitol. The C_2 symmetry of the substrate and the appropriate protection of the central diol unit are the crucial features for the high diastereofacial discrimination during the cycloaddition process.

Easily available compounds with C_2 symmetry are very convenient scaffolds for asymmetric two-directional syntheses. In a strategy based on the simultaneous homologation of both ends of a chain, the sense of chirality in the formation of new stereogenic centers may proceed with substrate control.[1]

γ-Hydroxymethyl α,β-butenolide derivatives of type **1** (Scheme 1) have been extensively used in the enantioselective synthesis of many molecules of biological significance.[2] Compounds **1** may be conveniently prepared from D-mannitol through sequences involving an oxidative cleavage step that yields a protected D-glyceraldehyde.[3] In most synthetic applications of **1**, a crucial transformation is the addition of a reagent to the carbon−carbon double bond, with concomitant creation of one or two new stereogenic centers. The diastereoselectivity of this addition process is not always high.

Scheme 1



(+)-Grandisol (**12**) is the main component of the sexual attracting pheromone of the cotton boll weevil, *Anthonomous grandis* Boheman, and other insects.[4] A total synthesis of **12** was developed in our laboratories.[5] A key step in this synthesis was the formation of the cyclobutane ring through a [2 + 2] photocycloaddition of ethylene to (*S*)-4-methyl-

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(1) For a review see: Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167.

(2) See ref 3 in: Sánchez-Sancho, F.; Valverde, S.; Herradón, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209.

(3) Mann, J.; Partlett, N. K.; Thomas, A. *J. Chem. Res., Synop.* **1987**, 369.

(4) (a) Tumlinson, J. H.; Hardee, D. D.; Gueldner, R. C.; Thompson, A. C.; Hedin, P. A.; Minyard, J. P. *Science* **1969**, *166*, 1010. (b) Tumlinson, J. H.; Gueldner, R. C.; Hardee, D. D.; Thompson, A. C.; Hedin, P. A.; Minyard, J. P. *J. Org. Chem.* **1971**, *36*, 2616.

(5) Alibés, R.; Bourdelande, J. L.; Font, J.; Parella, T. *Tetrahedron* **1996**, *52*, 1279. See references therein for other synthetic approaches to (±)-, (+)-, and (−)-grandisol.

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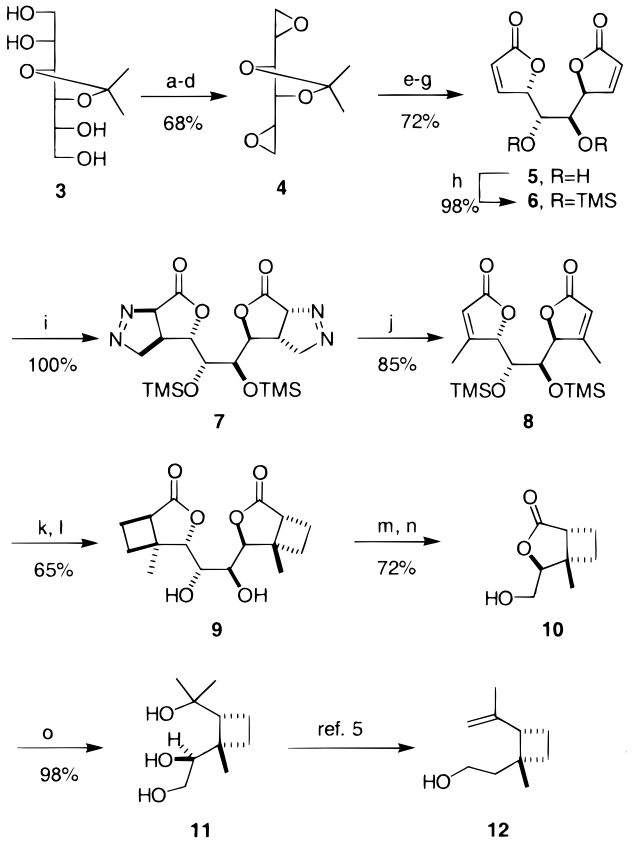
5-((pivaloyloxy)methyl)-2(5*H*)-furanone, a compound of type **1** that bears a methyl group at the *β*-carbonyl position. Although this reaction proceeded in good yield, the diastereofacial selectivity was low (24% de in favor of the *anti* cycloadduct).

Starting from D-mannitol, we have recently prepared several bis(α,*β*-butenolides), synthetically equivalent to **1**, with the general structure **2** but with opposite configuration at $C_5/C_{5'}$. We have evaluated the influence of the protecting groups of the central diol unit in the [2 + 2] photocycloaddition of ethylene to compounds **2**. The aim of this work was to improve the facial discrimination in relation to their single analogues **1**. Among the studied derivatives, that with bis(trimethylsilyl) protecting groups has proved to be the most effective, with an overall antifacial selectivity higher than 98%.[6]

Taking into account these previous results, we have now developed an alternative synthesis of (+)-grandisol from a C_2-symmetric bis(α,*β*-butenolide) that considerably improves the asymmetric induction during the photocycloaddition process. The synthetic pathway is shown in Scheme 2.

Scheme 2. Formal Synthesis of (+)-Grandisol



a) TBSCl, DMF, imidazole, rt, 1.25 h; b) MsCl, CH_2Cl_2, Et_3N, 0 °C, 30 min; c) n-Bu_4NF, THF, rt, 4 h; d) NaOH (aq), THF/MeOH, 0 °C, 30 min; e) $PhSeCHCO_2^{2-}$ (ref. 9); f) AcOH, Δ; g) H_2O_2, AcOH, THF, 0 °C; h) TMSIm, THF, rt, 4h; i) CH_2N_2, ether/THF, rt, 48 h; j) 1,4-dioxane Δ; k) C_2H_4, hν, acetone, -78 °C, 6 h; l) n-Bu_4NF, THF, rt, 16 h; m) $Pb(OAc)_4$, EtOAc, rt, 2 h; n) $NaBH_4$, EtOAc, rt, 2.5 h; o) MeLi, THF, -78 °C to rt, 2 h

The commercially available isopropylidene-D-mannitol derivative **3** was converted into the corresponding bis(epoxide) **4**[7] using known methodology. The bis(butenolide) **5**[8] ($[\alpha]^{20}_D = -140$, *c* 0.50, DMSO) was readily prepared from **4** in 72% overall yield, through the following sequence of reactions:[9] one-pot double addition of phenylselenoacetic acid dianion; acid-induced lactonization; oxidation of the selenide functions with consequent thermal elimination. Although intermediates were not isolated, control NMR analysis performed after each individual transformation demonstrated that the acetonide central protection was hydrolyzed during the oxidation step.

After silylation, the methyl groups at the *β*-carbonyl positions of the bis(butenolide) **6**[10] ($[\alpha]^{20}_D = -92.5$, *c* 1.06, $CHCl_3$) were introduced by treatment with diazomethane, followed by pyrolysis of the corresponding bis(pyrazoline) **7**[11] ($[\alpha]^{20}_D = -325.2$, *c* 2.12, $CHCl_3$), in 85% overall yield. Although the stereochemical outcome of the dipolar cycloadditon of diazomethane is not relevant for the synthesis, it is worth mentioning that the NMR spectrum of **7** showed a single diastereoisomer of high symmetry. This diastereoisomer was assigned as the *anti-anti* bis-cycloadduct, according to previous results.[12]

The bis(lactone) **8**[13] ($[\alpha]^{20}_D = -3.9$, *c* 1.03, $CHCl_3$) was then irradiated in a solution of acetone saturated with ethylene in a Pyrex vessel with a medium-pressure 125 W mercury lamp at −78 °C. The ^1H and ^{13}C NMR spectra of the crude reaction mixture showed a main set of signals,

(6) De March, P.; Figueredo, M.; Font, J.; Raya, J. *Tetrahedron Lett.* **1999**, *40*, 2205.

(7) Poitout, L.; Le Merrer, Y.; Depezay, J. C. *Tetrahedron Lett.* **1994**, *35*, 3293.

(8) (5*S*,5′*S*)-5,5′-[(1*R*,2*R*)-1,2-dihydroxyethane-1,2-diyl]bis[2(5*H*)-furanone] (**5**): mp 183−185 °C (MeOH); IR (KBr) 3430, 3392, 3093, 1750, 1180, 1103, 1046 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) *δ* 7.77 (dd, *J* = 5.5 Hz, *J*′ = 2.0 Hz, 1H), 6.25 (dd, *J* = 5.9 Hz, *J*′ = 2.0 Hz, 1H), 5.61 (d, *J* = 5.9 Hz, 1H), 5.28 (m, 1H), 3.68 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) *δ* 173.2, 156.4, 121.0, 84.1, 71.9; MS *m*/*z* 227 (3), 226 (3), 143 (88), 125 (57), 97 (55), 84 (92), 83 (100), 55 (59). Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 52.88; H, 4.58.

(9) Figueredo, M.; Font, J.; Virgili, A. *Tetrahedron* **1987**, *43*, 1881.

(10) (5*S*,5′*S*)-5,5′-[(1*R*,2*R*)-1,2-bis(trimethylsilyloxy)ethane-1,2-diyl]bis-[(2(5*H*)-furanone] (**6**): mp 101−103 °C (EtOAc/hexane); IR (KBr) 3107, 2959, 2903, 1764, 1257, 1159, 1096 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) *δ* 7.49 (dd, *J* = 5.8 Hz, *J*′ = 1.5 Hz, 1H), 6.10 (dd, *J* = 5.8 Hz, *J*′ = 2.2 Hz, 1H), 5.36 (m, 1H), 3.62 (d, *J* = 3.7 Hz, 1H), 0.10 (s, 9H); ^{13}C NMR (62.5 MHz, acetone-d_6) *δ* 172.8, 155.7, 121.5, 83.6, 75.5, 0.4; MS *m*/*z* 371 (2), 370 (7), 355 (6), 287 (14), 129 (38), 75 (100), 73 (90). Anal. Calcd for $C_{16}H_{26}Si_2O_6$: C, 51.86; H, 7.07. Found: C, 51.95; H, 7.12.

(11) (3a*S*,3a′*S*,4*S*,4′*S*,6a*R*,6a′*R*)-4,4′-[(1*R*,2*R*)-1,2-bis((trimethylsilyl)oxy)-ethane-1,2-diyl]bis[3a,4,6,6a-tetrahydro-3*H*-furo[3,4-*c*]pyrazol-6-one] (**7**): mp 165−167 °C (EtOAc/hexane); IR (KBr) 2959, 2924, 2853, 1778, 1257, 1229, 1180, 1124, 1039 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) *δ* 5.56 (dd, *J* = 9.5 Hz, *J*′ = 2.2 Hz, 1H), 5.19 (dd, *J* = 19.4 Hz, *J* = 9.9 Hz, 1H), 4.76 (ddd, *J* = 19.4 Hz, *J*′ = 4.4 Hz, *J*″ = 2.2 Hz, 1H), 4.38 (m, 1H), 3.57 (d, *J* ≈ 3.6 Hz, 1H), 2.84 (tdd, *J* = 9.7 Hz, *J*′ = 4.4 Hz, *J*″ = 2.2 Hz, 1H), 0.16 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 167.5, 92.5, 87.1, 84.3, 76.8, 34.2, 0.3; MS *m*/*z* 454 (0.5), 239 (12), 195 (53), 73 (100). Anal. Calcd for $C_{18}H_{30}N_4Si_2O_6$: C, 47.55; H, 6.65; N, 12.32. Found: C, 47.47; H, 6.60; N, 12.24.

(12) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A.; Parella, T. *Tetrahedron* **1996**, *52*, 1267.

(13) (5*S*,5′*S*)-5,5′-[(1*R*,2*R*)-1,2-bis(trimethylsilyloxy)ethane-1,2-diyl]bis-[4-methyl-2(5*H*)-furanone] (**8**): oil; IR (KBr) 2957, 2922, 1766, 1647, 1255, 1121 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) *δ* 5.85 (br s, 1H), 5.16 (br s, 1H), 3.87 (s, 1H), 2.06 (br s, 3H), 0.08 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 173.0, 165.8, 118.8, 82.3, 71.8, 14.4, 0.3; MS *m*/*z* 383 (4), 301 (32), 183 (29), 73 (100). Anal. Calcd for $C_{18}H_{30}Si_2O_6$: C, 54.24; H, 7.59. Found: C, 53.93; H, 7.55.

consistent with a highly symmetric bis(cyclobutane) adduct, along with traces of other reaction products. This material was directly hydrolyzed by treatment with tetra-*n*-butylammonium fluoride, and the corresponding diol **9**[14] ($[\alpha]^{20}_D = +18.0$, *c* 0.50, $CHCl_3$) was isolated in 65% yield for the two steps. In all these transformations the stereochemical integrity of the intermediates was preserved, as evidenced by the simplicity of their NMR spectra, in agreement with their high symmetry. The cleavage of compound **9** was accomplished by consecutive treatment with lead tetraacetate and sodium borohydride in a one-pot procedure. The single hydroxymethyl lactone **10** was isolated in 72% yield. This correlation demonstrates the *anti-anti* stereochemistry of the precursor bis(cyclobutane) **9**. The *syn* diastereoisomer of **10**, coming from the opposite facial approach to the butenolide during the ethylene photocycloaddition, was not detected. The addition of an excess of methyllithium to lactone **10** gave a 98% yield of the triol **11**, which had been previously converted in (+)-grandisol (**12**).[5]

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(14) (1*R*,1′*R*,4*S*,4′*S*,5*S*,5′*S*)-4,4′-[(1*R*,2*R*)-1,2-dihydroxyethane-1,2-diyl]-bis[5-methyl-3-oxabicyclo[3.2.0]heptan-2-one] (**9**): mp 180−182 °C (EtOAc/hexane); IR (KBr) 3507, 2966, 2931, 2875, 1743, 1335, 1307, 1180, 1089, 997 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.20 (s, 1H), 3.85 (s, 1H), 3.04 (br s, 1H), 2.71 (br d, $J = 8.8$ Hz, 1H), 2.51 (dq, $J = 11.7$ Hz, $J' \approx 9.5$ Hz, 1H), 2.26 (dt, $J = 11.0$ Hz, $J' \approx 9.5$ Hz, 1H), 2.00 (ddt, $J = 11.7$ Hz, $J' = 9.5$ Hz, $J'' \approx 2.2$ Hz, 1H), 1.85 (ddt, $J = 11.0$ Hz, $J' = 9.5$ Hz, $J'' \approx 2.9$ Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 181.1, 86.2, 70.9, 44.1, 43.9, 32.1, 21.8, 17.8; MS *m*/*z* 311 (1), 84 (100), 81 (52), 55 (37), 41(39). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.16; H, 7.34.