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Stereoselective Approach to the BCD Framework of Richardianidins via Intramolecular Reformatsky-Type Reaction Promoted by Diethylaluminum Chloride

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Abstract: The tricyclic derrivative (**10d**) has been prepared by intramolecular Reformatsky addition of α-bromopropionate (**8b**) in the presence of diethylaluminum chloride and activated Zn. Transformation of (**10d**) into the tricyclic methyl ketone (**12a**) was accomplished by dehydration followed by oxidation under Wacker conditions with 75% overall yield. © 1997 Elsevier Science Ltd.

The novel 6,7-seco-6,11-cyclolabdane skeleton is present in richardianidins **1** and **2**, two constituents of the leaves of the toxic plant *Cluytia richardiana* (L.) family Euphorbiaceae, which grows in the mountainous regions of western and southern Saudi Arabia.[1] These two secolabdanes bear an obvious structural relationship to other labdane-type diterpenes, including saudin **3**[2] and nepetaefolin **4**.[3] Saudin has been claimed to develop hypoglucemic activity when administrated to alloxanized mice and several *Cluytia* species are widely used in folk medicine and are of potential medicinal value[4] (Fig 1).

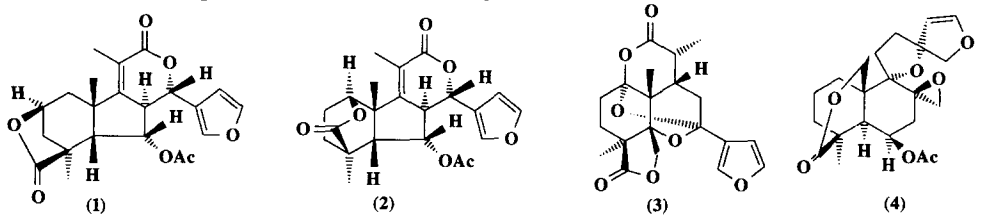
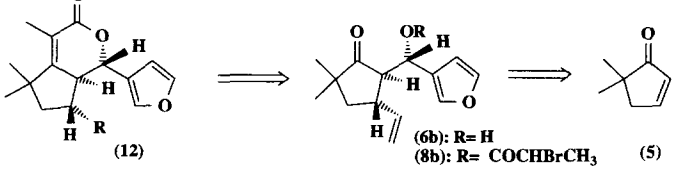


Fig.1

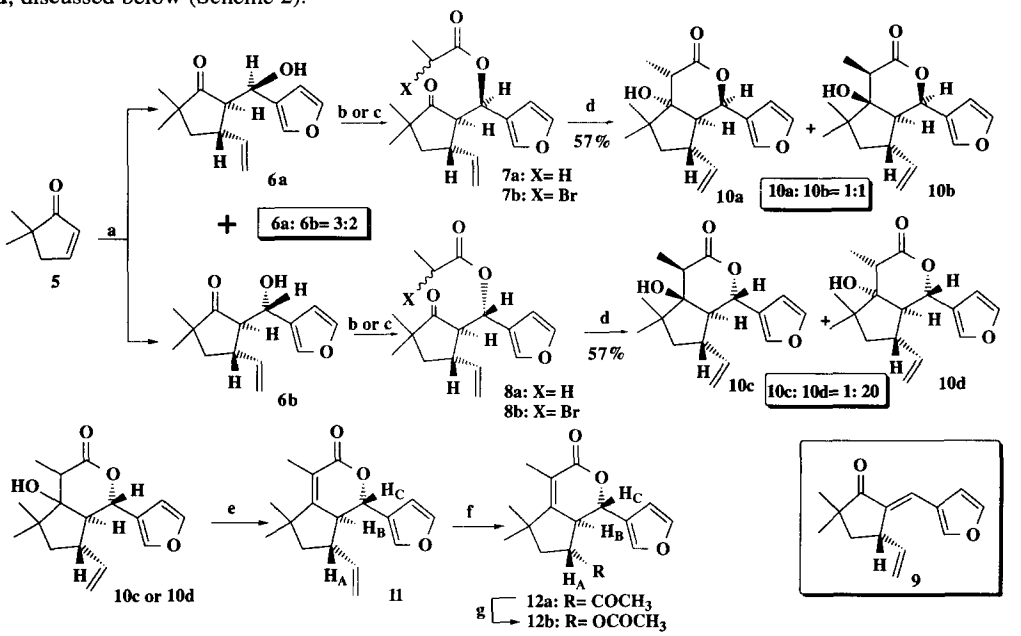
In the course of studies directed towards the synthesis of **1** and **2**, we envisaged a novel synthetic strategy to access to the furanoid bicyclo[4.3.0]nonane nucleus (**12**) present in both natural diterpenes.

The synthesis of **12** was devised (Scheme 1) via intramolecular Reformatsky addition of the keto bromopropionate **8b**, easily accessible from the hydroxy precursor **6b**. The all *trans* stereochemistry of the keto hydroxy derivative **6b** would be obtained by tandem copper-catalyzed addition of vinyl magnesium bromide to the 5,5-dimethyl-2-cyclopentenone **5**[5] and subsequent trapping of the enolate with 3-furaldehyde.



Scheme 1

Treatment of 5,5-dimethyl-2-cyclopentenone **5** with bromomagnesium divinylcuprate (formed from 2 equiv of vinylmagnesium bromide and 1 equiv of CuI)[6] allowed introduction of the vinyl group with concomitant generation of the corresponding enolate, which was trapped by reaction with 3-furaldehyde to afford a mixture of ketols **6a**: **6b**= 3:2 in 70% isolated yield.[7] The major product **6a**, m.p. 72-74°C (hexane), was isolated from the crude mixture by crystallization in hexane. The structural assignment of both ketols **6a** and **6b** was made based on spectroscopic analysis and chemical correlations with the tricyclic derivatives **10a-10d**, discussed below (Scheme 2).[8]



a: i: $(CH_2=CH)MgBr$ (2 eq.), CuI (1 eq.), THF, -78 °C; ii: 3-furaldehyde; **b**: ClCOEt, pyr, 0 °C; **c**: $ClCOCHBrCH_3$, pyr, 0 °C; **d**; Et_2AlCl, Zn, $CuBr_2{\cdot}SMe_2$, THF, 15h.; **e**: Cl_2SO, pyr, 0 °C; **f**: $PdCl_2$, CuCl, DMF, H_2O, O_2, 96%; **g**: See ref.12.

Scheme 2.

Acylation (propionyl chloride, or α–bromopropionyl chloride, pyridine at 0 °C) of **6a** furnished the propionate **7a** or the bromopropionate **8a**, with quantitative yields. Under the same conditions, the ketol **6b** also led quantitatively either to the propionate **7b** or the bromopropionate **8b**. Several cyclization attempts performed on propionates **7a** and **7b** (LDA; $TfOBnBu_2$/ Et_3N) led exclusively to the elimination product **9** (Scheme 3). We found that the desired cyclization could be smoothly achieved by exposing the bromopropionates **8a** or **8b** to diethylaluminum chloride and activated Zn in THF according to the procedure reported by Yamamoto and col.[9]

Treatment of **8a** with diethylaluminum chloride and zinc together with a catalytic amount of $CuBr{\cdot}SMe_2$ at room temperature led to a mixture of hydroxy esters **10a**: **10b**= 1: 1 with 57% yield. Analogous conditions applied to **8b** led to the diastereoisomeric mixture **10c**: **10d**= 1: 20 with 60% yield. Isolation of the four diastereomeric hydroxy esters was accomplished by flash chromatography of the crude reaction mixtures. Structural assignments were made based on resonance experiments and the chemical behaviour under dehydration conditions.

The major formation of **10d** from **8b** may be rationalized in terms of the encounter of the *Re* and *Si* reacting faces by the *ul* intramolecular approach of the aluminum Z-enolate of the ester to the carbonyl function.[10]

Reaction of either **10c** or **10d** with $SOCl_2$ and pyridine at 0 °C led exclusively to the α,β-unsaturated ester **11**, m.p. 116-118 °C (hexane), with 85% and 77% yields, respectively. The high J values obtained for the three vecinal protons ($J_{A/B}$= $J_{B/C}$= 12 Hz) together with the noe experiments performed on **11** and **12a**, showed that H_A, H_B and H_C were all *trans*, thus confirming the relative configuration depicted in Scheme 2.

Oxidation of the vinyl moiety under Wacker conditions[11] led to the isolation of the methyl ketone **12a**, m.p.163-165 °C (hexane), with 96% yield. However, the methyl ketone **12a** was reluctant to undergo the Baeyer-Villiger oxidation to **12b** under different conditions.[12] The presence of the furan ring close to the carbonyl function in **12a** resulted to be an insourmountable hurdle for our purposes: the activation of the carbonyl function under acidic conditions was followed by nucleophilic attack of the furane moiety; further transformations under the reaction conditions led to the formation of tetracyclic derivative **13**[13], whose presence has been detected by ^{1}HNMR analysis of the crude. Under basic conditions ($NaHCO_3$), the treatment with peracids led to the recovery of the starting material.

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4. Mahunnah, R. L. A.; Mtotmwema, K., *J. Econ. Tox. Bot.*, **1985**, *7*, 505.
5. Creger, P. L. , *J Am. Chem. Soc.*,**1967**, *89*, 2500.
6. Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. *J. Am. Chem. Soc.*, **1981**, *103*, 4647-4648.
7. The ample precedent for *syn* selective aldol reactions of transition metal enolates is well known in the literature: the vicinal coupling constant J_{AC}= 3.8 Hz is less for the *syn* isomer (**6a**) than for the *anti* isomer (**6b**) (J_{AC}= 5.4 Hz) as already reported for similar systems. For a review see: Heathcock, C. H. in "Asymmetric synthesis", Academic Press 1984. Morrison, J. D. Ed. Vol. #3, Chapter 2.
8. All new compounds were characterized by spectroscopic methods. Correct microanalytical data have also been obtained. For example:

   6a: IR (film) ν_{max} : 3470, 1736, 1647 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 0.80 (s, 3H); 1.07 (s, 3H); 1.52 (t, J= 12 Hz, 1H); 1.84 (dd, J= 12 Hz, J= 6 Hz, 1H); 2.52 (t, J= 3.8 Hz, 1H); 2.55 (m, 1H); 4.90 (d, J= 3.8 Hz, 1H); 5.05 (m, 2H); 5.66 (m, 1H); 6.23 (m, 1H); 7.31 (m, 2H) ppm. ^{13}CNMR: δ($CDCl_3$): 23.23 (q); 24.44 (q); 38.99 (d); 43.58 (t); 45.59 (s); 59.27 (d); 66.03 (d); 109.11 (d); 115.37 (t); 126.36 (s); 139.80 (d); 140.01 (d); 143.70 (d); 224.41 (s) ppm. MS (EI) (m/z, %): 234 (55); 138 (53); 123 (100); 97 (82).

   6b: IR (film) ν_{max} : 3464, 1734, 1640 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 0.88 (s, 3H); 1.05 (s, 3H); 1.49 (t, J= 12 Hz, 1H); 1.84 (dd, 1H, J= 12 Hz, J= 6 Hz, 1H); 2.38 (dd, J= 11 Hz, J= 5.4 Hz, 1H) 2.54 (m, 1H); 4.88 (d, J= 5.4 Hz, 1H); 4.91 (m, 2H); 5.61 (m, 1H); 6.32 (m, 1H);7.29 (m, 1H); 7.30 (m, 1H) ppm. ^{13}CNMR: δ($CDCl_3$): 23.87 (q); 24.55 (q); 40.03 (d); 43.37 (t); 45.53 (s); 59.79 (d); 67.18 (d); 109.41 (d); 115.05 (t); 126.39 (s); 139.83 (d); 140.59 (d); 143.01 (d); 222.77 (s). MS (EI) (m/z, %): 234 (19); 138 (50); 123 (90); 97 (80); 53 (75).

10a: IR (film) ν_{max}: 3455, 1726, 1642 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 0.85 (s, 3H); 1.04 (s, 3H); 1.32 (d, J= 7 Hz, 3H); 1.60 (m, 2H); 2.45 (dd, J= 10 Hz, J= 5 Hz, 1H); 2.60 (m, 1H); 2.92 (q, J= 7 Hz, 1H); 4.79 (m, 2H); 5.56 (m, 1H); 5.67 (d, J= 5Hz, 1H); 6.30 (m, 1H); 7.37 (m, 2H) ppm. ^{13}CNMR: δ($CDCl_3$): 11.87 (q); 23.23 (q); 23.47 (q); 39.63 (d); 40.58 (d); 45.29 (s); 45.75 (t); 56.78 (d); 72.73 (d); 83.07 (s); 109.17 (d); 114.31 (t); 122.70 (s); 139.40 (d); 141.11 (d); 143.19 (d); 174.84 (s) ppm. MS (EI) (m/z, %): 272 (34); 213 (65); 95 (100).

10b: m.p. 178-180 °C (hexane). IR (film) ν_{max} : 3470, 1736, 1630 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 1.03 (s, 3H); 1.11 (s, 3H); 1.32 (m, 1H); 1.39 (d, J= 7 Hz, 3H); 1.63 (m, 1H); 2.33 (dd, J= 10 Hz, J= 5 Hz, 1H); 2.59 (m, 1H); 2.95 (q, J= 7 Hz, 1H); 4.55 (m, 2H); 5.27 (m, 1H); 5.59 (d, J= 5 Hz, 1H); 6.28 (m, 1H); 7.32 (m, 1H); 7.43 (m, 1H) ppm. ^{13}CNMR: δ($CDCl_3$): 9.37 (q); 23.06 (q); 24.21 (q); 41.54 (d); 45.26 (d); 46.58 (s); 47.55 (t); 60.49 (d); 72.16 (d); 84.10 (s); 109.29 (d); 113.85 (t); 121.42 (s); 139.38 (d); 141.05 (d); 142.91 (d); 174.27 (s) ppm. MS (EI) (m/z, %): 290 (11); 194 (32); 137 (87); 95 (86); 81 (93); 69 (92).

10c: IR (film) ν_{max} : 3437, 1738, 1651, 1155 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 1.08 (s, 3H); 1.15 (s, 3H); 1.28 (d, J= 7 Hz, 3H); 1.49 (dd, J= 12 Hz, J= 6 Hz, 1H); 1.75 (t, J= 12 Hz,1H); 2.48 (d, J= 10 Hz, 1H); 2.68 (m, 1H); 2.87 (q, J= 7 Hz, 1H); 5.08 (dd, J= 10 Hz, J= 3.4 Hz, 1H); 5.73 (m, 1H); 6.48 (m, 1H); 7.45 (m, 1H); 7.51 (m, 1H) ppm.

10d: m.p. 112-114 °C (hexane) ; IR (film) ν_{max} : 3400, 1727, 1645 cm^{-1}. ^{1}H NMR: δ($CDCl_3$): 1.14 (s, 6H); 1.31 (d, J= 7 Hz, 3H); 1.55 (dd, J= 12 Hz, J= 6 Hz, 1H) 1.87 (t, J= 12 Hz, 1H); 2.23 (d, J= 12 Hz, 1H); 2.25 (m, 1H); 2.98 (q, J= 7Hz, 1H); 4.60 (m, 2H); 5.00 (d, J= 11 Hz, 1H); 5.32 (m, 1H); 6.44 (m, 1H); 7.38 (m, 1H); 7.45 (m, 1H) ppm. ^{13}CNMR: δ($CDCl_3$): 8.65 (q); 23.87 (q); 25.23 (q); 40.67 (d); 42.94 (d); 45.61 (s); 48.03 (t); 61.91 (d); 75.14 (d); 83.74 (s); 109.60 (d); 114.31 (t); 122.07 (s); 140.36 (d); 140.83 (d); 143.57 (d); 174.44 (s) ppm. MS (EI) (m/z, %): 290 (38); 193 (45); 121 (59); 95 (87); 81 (100) ppm.

11: IR (film) ν_{max}: 1737, 1640 cm^{-1}. ^{1}H NMR: δ($CDCl_3$): 1.29 (s, 3H); 1.30 (s, 3H); 1.58 (t, J= 12 Hz, 1H); 1.76 (dd, J= 12 Hz, J= 6 Hz, 1H); 1.98 (d, J= 3 Hz, 3H); 2.30 (m, 1H); 2.74 (tq, J= 12 Hz, J= 3 Hz, 1H); 4.68 (m, 2H); 4.94 (d, J= 12 Hz, 1H); 5.24 (m, 1H); 6.40 (m, 1H); 7.35 (m, 1H); 7.38 (m, 1H) ppm. ^{13}CNMR: δ($CDCl_3$): 12.39 (q); 26.60 (q); 27.06 (q); 41.59 (s); 43.96 (d); 50.03 (t); 51.78 (d); 76.36 (d); 109.41 (d); 114.99 (t); 120. 19 (s); 122.60 (s); 138.80 (d); 141.22 (d); 143.29 (d); 166. 12 (s); 166.85 (s) ppm. MS (EI) (m/z, %): 272 (13); 176 (100); 161 (40); 133 (67), 91 (58); 69 (40).

12a: IR (film) ν_{max}: 1707, 1694 cm^{-1}. ^{1}H NMR: δ($CDCl_3$): 1.29 (s, 3H); 1.31 (s, 3H); 1.67 (t, J= 12 Hz, 1H); 1.81 (s, 3H); 1.89 (dd, J= 12 Hz, J= 6 Hz, 1H);1.98 (d, J= 3 Hz, 3H); 2.71 (m, 1H); 3.47 (tq, J= 11 Hz, J= 3 Hz, 1H); 4.86 (d, J= 11 Hz, 1H); 6.40 (m, 1H); 7.35 (m, 1H); 7.41 (m, 1H) ppm. ^{13}CNMR: δ($CDCl_3$): 12.39 (q); 26. 12 (q); 26.87 (q); 29.70 (q); 42.76 (s); 47.37 (t); 49.68 (d); 50.84 (d); 75.91 (d); 109.17 (d); 120.03 (s); 121.93 (s); 141.06 (d); 143.60 (d); 165.20 (s); 166.58 (s); 207.77 (s) ppm. MS (EI) (m/z, %): 288 (50); 245 (75); 149 (95); 91 (50); 69 (45).

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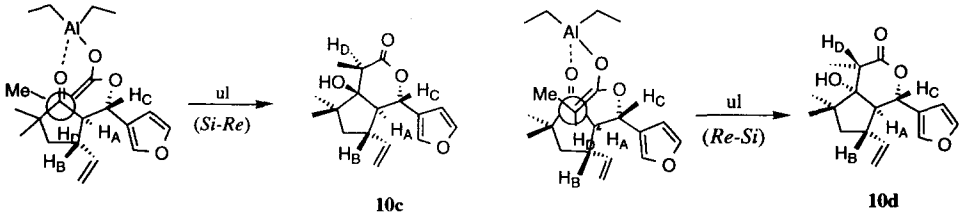
10. The 1,3 interaction with the vinyl residue may be responsible for the interaction of the enolate with the carbonyl functionality from the β side in the transition state leading to the major product, **10d**.



10c **10d**

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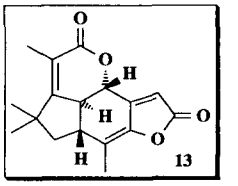
12. Treatment of **12a** with either m-chloroperbenzoic acid or trifluoroperacetic acid led to complex mixtures of difficult resolution. Reaction with magnesium monoperoxyphthalate, urea-hydrogen peroxide (UHP) or permaleic acid led to the recovery of the starting material. Likewise, treatment of **12a** with tert-butyl hydroperoxide under basic conditions also failed.

13. The formation of **13** may be easily rationalized in terms of the nucleophilic attack of the furan moiety on the activated carbonyl function followed by oxidative transformations.



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