Pergamon

Tetrahedron Letters, Vol. 35, No. 23, pp 3937-3940, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0736-H

A *C-B-A-D* Approach to Brassinosteroids; Obtention of a *C*-Ring Precursor from Pyridine

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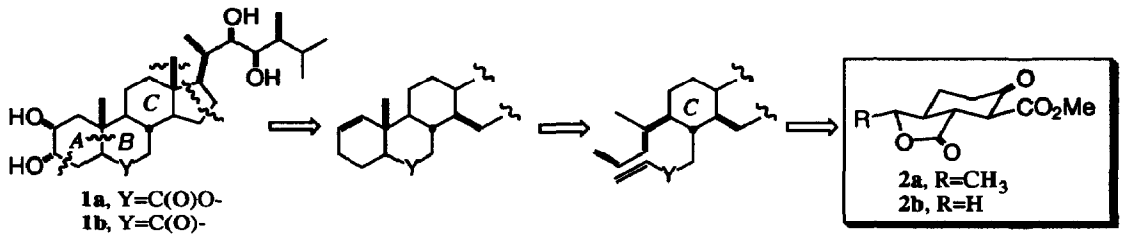
Abstract: *The potassium salt of glutaconaldehyde, a degradation product of pyridine, has been converted, via inter alia IMDA cyclisation of a dienyl fumaric ester and baker's yeast-mediated reduction of a ketoester, into an optically-active 2,3,4-trisubstituted cyclohexanone having a stereochemical pattern strongly related to that displayed by the C-ring in the title compounds.*

Brassinolide, **1a**, and castasterone, **1b**, are representative members of a class of natural steroids, i.e. brassinosteroids, displaying hormone activity in plants.[1-3] These growth-regulating agents appear to have great promise in agriculture; plant responses to treatment with **1a** include a significant increase in grain crops. More recently, **1a** has been shown to display some pheromone activity.[2] The natural abundance of these phytohormones being extremely low, numerous synthetic routes starting from such readily accessible steroids as stigmasterol and ergosterol have been explored.[3] However, no total synthesis of either **1a** or **1b** has been attempted to date, such a venture having been judged as "only of theoretical interest since it requires the formation of the exceptionally complex stereochemistry of these considered compounds which contain 13 chiral centres".[3] Challenged by this statement, we embarked upon a total synthesis of either **1a** or **1b** by first concentrating our efforts on the preparation of a cyclohexane derivative featuring the *C*-ring. Accurate control of the relative configuration of the chiral centres during the elaboration of **2a** was considered to be the key to a straightforward generation of the *C-B-A* ring system by an intramolecular Diels-Alder (IMDA) reaction .



1a, Y=C(O)O-
1b, Y=C(O)-

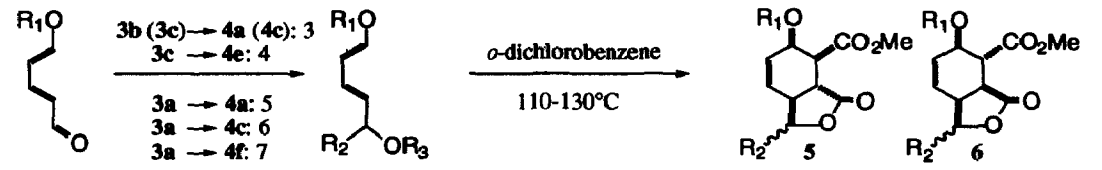
2a, R=CH_3
2b, R=H

Starting from the predicted IMDA product, it should then be possible to generate a *D*-ring appended to the C-14 side-chain by means of free-radical allylation methodology.[4] An efficient access to both ketoesters **2a** and **2b** is described herein, further transformation of **2a** into a tricyclic derivative being reported in the accompanying papers.

Previously, it was shown that a lactone related to **2a** could be prepared in a few steps from pyridine.[5,6] Treatment of the pyridine-SO_3 complex with KOH resulted in the formation of the potassium salt of glutaconaldehyde, **3a**. Condensation of **3a** with benzoyl chloride,[6a] followed by reduction of the resulting aldehyde, **3b**, with $NaBH_4$, furnished the alcohol **4a** (64%; 87% overall, by performing an *in situ* reduction) from which fumarate **4b** (98%) could be derived by condensation with the chloride of the monomethyl ester of fumaric acid (FMMECl). Heating a solution of **4b** in *o*-dichlorobenzene at 110°C for 3 hours resulted in the formation of a single lactone, strongly resembling (^{1}H NMR) the corresponding ethyl ester[6c] and to which structure **5a** was ascribed.

Conversion of **5a** into **2b**, by performing *inter alia* mild saponification (K_2CO_3/MeOH, 0-10°C), proved unfeasible

as elimination of the benzoate group occurred. Moreover, attempted condensation of **3b** with methyllithium (1 eq., ether, -78°C) in order to prepare the lactone **2a** resulted in extensive degradation.



2 [**3a**, R_1=K ; **3b**, R_1=C(O)-Ph ; **3c**, R_1=C(O)-O-Allyl] 1

* *acronym for fumaroyl, monomethyl ester*

8 [**4a**, R_1=C(O)-Ph; R_2=R_3=H ; **4b**, R_1=C(O)-Ph; R_2=H; R_3=FMME*]

8 [**4c**, R_1=C(O)-O-Allyl; R_2=R_3=H ; **4d**, R_1=C(O)-O-Allyl; R_2=H; R_3=FMME]

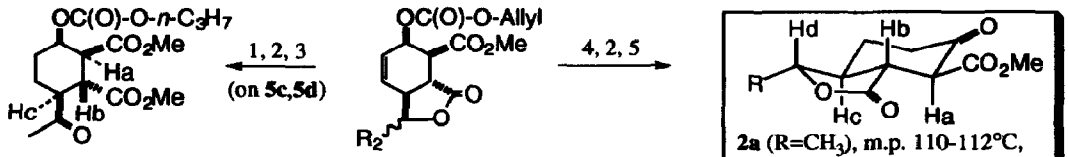
8 [**4e**, R_1=C(O)-O-Allyl; R_2=CH_3; R_3=H ; **4f**, R_1=C(O)-O-Allyl; R_2=CH_3; R_3=FMME]

5a, 6a, R_1=C(O)-Ph; R_2=H
5b, 6b, R_1=C(O)-Allyl; R_2=H
5c, 6c, R_1=C(O)-Allyl; R_2=α-CH_3
5d, 6d, R_1=C(O)-Allyl; R_2=β-CH_3

1- PhC(O)Cl (1 eq.), dioxan, r.t., 1 hour; 2- allyl chloroformate (1 eq.), dioxan, r.t., 0.5 hour; 3- $NaBH_4$ (1 eq.), dioxan, r.t., 24 hours; 4- MeLi-LiBr (1 eq.), ether, -78°C, 0.5 hour; 5- 1 then 3 (*in situ*); 6- 2 then 3 (*in situ*); 7- *i)* allyl chloroformate (1 eq.), ether, r.t., 3 hours; *ii)* 4 (*in situ*); *iii)* FMMECl (1 eq., *in situ*), -78°C, 2 hours, then r.t., 2 hours; 8- FMMECl (1 eq.), pyridine (1.1 eq.), CH_2Cl_2, -15°C, 3 hours.

Among the various esters which were consequently examined, the carbonate **3c** proved suitable. To verify that the stereoselectivity of the cyclisation step would not be affected, **3a** was treated with allyl chloroformate; the resulting aldehyde **3c** (77%) being subsequently reduced by $NaBH_4$ to the alcohol **4c** (56%; 91% overall in a one-pot procedure). Treatment of **4c** with FMMECl (1 eq.) and pyridine (1 eq.) in CH_2Cl_2 gave fumarate **4d** which smoothly cyclised in hot *o*-dichlorobenzene ([**4d**]=0.03 M, 130°C, 3 hours) to give, after flash-chromatography (silica gel, hexane/AcOEt), the crystalline lactone **5b** [7] (85 %). ^{1}H NMR data of **5b** fitted well with that of the related benzoate and strongly supported the depicted *endo* structure.[8] The isomeric *exo* product, **6b**, was not detected. Conversion of lactone **5b** into the ketoester **2b** was then performed in high yield (92%) by removal of the carbonate group with 2-ethylhexanoic acid under palladium catalysis,[9] hydrogenation (H_2 (1 atm.), 5% Pd/C, AcOEt, r.t.) and finally Jones' oxidation (CrO_3 (2.5 eq.), 1/10 10N H_2SO_4/acetone, -15°C-r.t., 1.5 hour).

The formation of the *endo* product being ascertained, preparation of the lactone **2a** was then attempted. Condensation of **3c** with the MeLi-LiBr complex[10] (in ether), followed by esterification of the resulting alcohol, **4e**, with FMMECl furnished the fumarate **4f** in low yield (12%); a result of the low stability of **4e**. Indeed, pure **4f** was obtained in fair yield (45% overall) by adding to a suspension of **3a** in ether successively: *i)* allyl chloroformate (1 eq., r.t., 3h), *ii)* the MeLi-LiBr solution (1 eq., -78°C, 0.5 h), *iii)* FMMECl (1 eq., -78°C, 0.5 h, then r.t., 2 h). Upon heating in *o*-dichlorobenzene (130°C, 5 hours, [**4f**]=0.019 M), **4f** gave an approximately 16:4:1 (NMR) mixture of three isomeric lactones from which the major constituent, which proved to be **5c**, was isolated as white crystals (63%) by flash-chromatography (silica gel, hexane/ether). An oily fraction (20%) containing two other lactones (4:1 ratio, by ^{1}H NMR) was also separated.



7, m.p. 64-66°C, J_{ab}11.5Hz, J_{bc}11.9Hz

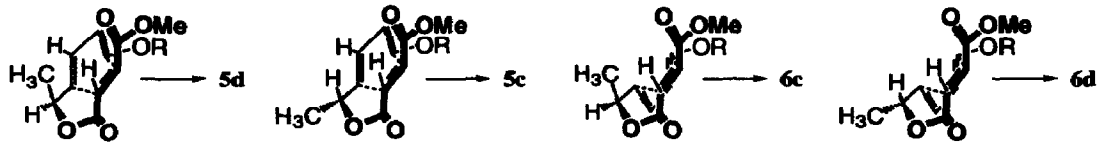
5b-d

2a (R=CH_3), m.p. 110-112°C, J_{ab}13Hz, J_{bc}13Hz, J_{cd}10.5Hz
2b (R=H), m.p. 130-131°C, J_{ab}13Hz, J_{bc}14Hz, J_{cd}11Hz

1- MeOH, CSA (0.1 eq.), 2 days; 2- H_2 (1 atm.), 5% Pd/C, AcOEt, r.t., 2 hours; 3- PCC (1 eq.), CH_2Cl_2, 0-10°C, 2 hours; 4- 2-ethylhexanoic acid (1.1 eq.), $Pd(Ph_3)_4$ (0.02 eq.), PPh_3 (0.08 eq.), CH_2Cl_2, r.t., 2 hours; 5- Jones' reagent, acetone, r.t., 1.5 hour)

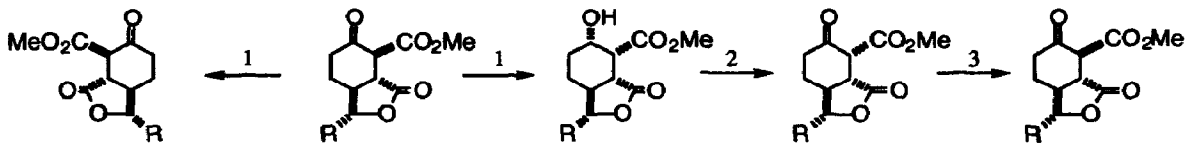
Each fraction was treated with methanol and camphorsulfonic acid. Opening of the lactone ring was fast with both **5c** and the major constituent of the oily product, which could be indicative of a *trans* ring junction.[6d] Moreover, oxidation of the hydroxyester thus formed from **5c** gave a ketone, **7**, identical (^1H,^{13}C NMR) to the major ketone formed under the same conditions from the oily component. It thus appears that the IMDA reaction proceeds to give predominantly the *endo* products.

Finally, the target lactone **2a** was prepared from **5c** in good yield (82% overall) by palladium-catalysed deprotection, hydrogenation, and Jones' oxidation. Coupling constants in the NMR spectrum, *vide supra*, for the protons borne by the chiral carbon atoms of **2a** substantiate both the *endo* structure of the major cyclisation product -i.e. **5c**- and the pseudo-equatorial position of the methyl substituent in this isomer. Examination of the transition-state models shown below provides a rationale for the observed stereochemical outcome of the cyclisation step, the methyl group appearing more strained in the postulated ENDO-AX transition state than in the ENDO-EQ one.



ENDO-AX ENDO-EQ EXO-AX EXO-EQ

A solution for preparing optically active **2a** emerges from these results since cyclisation of (*S*)-**4f** should give a lactone, **5c**, having the required absolute configuration.[11] Given however the practicability of the present process (5g-scale preparations of the lactones **2** have been performed routinely) the initial plan was pursued and **2b** first used as the model substrate, and subsequently **2a** were submitted to baker's yeast-mediated reduction. The proclivity of the enzymes involved in these reductions to direct selectively the addition of a hydride species onto the *re*-face of the keto group of related ketoesters is well-established.[12] Submission of either **2b** or **2a** to standard conditions[12b] and stirring the broth for 4 days at 35°C, followed by thorough extraction with AcOEt and column chromatography (silica gel, hexane/AcOEt) resulted in the isolation of a new hydroxyester, *(-)*-**8a** (res. *(-)*-**8b**), besides the unchanged ketone *(+)*-**2a** (res. *(+)*-**2b**).[13] Final adjustment of the stereochemistry was selectively realised by Jones' oxidation, then epimerisation of the resulting ketone, **9a** (res. **9b**), by treatment with a catalytic amount of imidazole in $CHCl_3$. The optical purities, as estimated by HPLC analysis (Chiralcel column, *i*-propanol/hexane), are only modest (e.g. *(-)*-**2a**: e.e.=78%) but could be optimised by submitting the *levo* ketoester to the same reducing conditions.



(+)-**2a**, $[\alpha]_D^{25}$ +30 *(rac.)*-**2a,b** *(-)*-**8a**, $[\alpha]_D^{25}$ -21 *(-)*-**2a**, $[\alpha]_D^{25}$ -39
(+)-**2b**, $[\alpha]_D^{25}$ +32 *(-)*-**8b**, $[\alpha]_D^{25}$ -33 *(-)*-**2b**, $[\alpha]_D^{25}$ -55

1- Baker's yeast, sucrose, pH 7 phosphate buffer, 35°C, 4 days; 2- Jones' reagent, acetone, 10-15°C, 1 hour; 3- imidazole (0.1 eq.), $CHCl_3$, r.t., 1 day.

In conclusion, the IMDA reaction of derivatives of glutaconaldehyde has been confirmed as a powerful means for preparing stereoselectively tetrasubstituted cyclohexene derivatives. Proper choice of experimental conditions has resulted in a convenient preparation of a key intermediate of our planned synthesis.

Acknowledgements: Thanks are due to La Fondation Roussel for a grant (to L.B.).

References and Notes

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2- Cutler, H.G. *ACS Symp. Ser.* **1991**, *474*, 334-345.

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4- Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1990**, *31*, 539-543.

5- Berthon, L. Dissertation, Paris (1990).

6- a) Baumgarten P. *Chem. Ber.* **1924**, *57*, 1622-1627; b) Becher J. *Organic Syntheses* **1980**, *59*, 79-83; c) The method we used for preparing the lactones **5** is largely inspired from the described (without experimental details or yield data however) thermal cyclisation of **4b** (Ingendoh, A.; Becher, J.; Clausen, H.; Nielsen, H. C. *Tetrahedron Lett.* **1985**, *26*, 1249-1252. The protocols we report herein stemmed from a thorough study of the experimental conditions.[5] Particularly crucial for reproducibility of the yields were: *i*) the use of the anhydrous potassium salt **3a** freshly recrystallised from methanol (m.p. 325°C); *ii*) the use of distilled (over CaH_2, under argon) *o*-dichlorobenzene and its removal at r.t. in a vacuum (10^{-2} τ); *iii*) purification of the fumarates on 60H silica gel (Merck) washed with aqueous $NaHCO_3$, then with water, and dried at 120°C in an oven before use; d) for related IMDA reactions, see: White, J.D.; Sheldon, S.G. *J. Org. Chem.* **1981**, *46*, 2273-2279 (see, also: Gschwend, H. W.; Lee, A.O.; Meier, H.-P. *J. Org. Chem.* **1973**, *38*, 2169-2173).

7- Selected melting points (uncorrected): **4d**: 70-72°C (ether); **5b**: 97-99°C (ether).

8- The term *endo* refers throughout to a major directing effect of both the carbomethoxy and the carbonate group.

9- Jeffrey, P.D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587-590.

10- *Experimental*: To a stirred suspension of **3a** (18.75g; 0.13 mol) in ether (350 ml), allyl chloroformate (14.7 ml; 0.13 mol) was added under argon. After 3 hours (or disappearance of the 364nm absorption maxima in UV (ethanol)), the mixture was cooled to -70°C then treated by a 1.5 M solution of the MeLi-LiBr complex (other organometallic species proved unsatisfactory) in ether (86.7 ml; 0.13 mol). After 30 min (or disappearance of the 272nm maxima in UV), freshly distilled FMMECl (19.3 g, 0.13 mol) was added dropwise to the heterogeneous mixture. After 30 min, the cooling bath was removed and the stirring was pursued for two hours. The mixture was then poured into a vigorously stirred mixture of KH_2PO_4 (6g), KOH (1g), iced brine (320g), and ether (185 ml). After 2 hours, the aqueous layer was extracted with ether (3x10 ml), the combined organic phases then being washed with saturated brine (10 ml), and dried (Na_2SO_4). Evaporation was followed by chromatography on $NaHCO_3$-washed 60H silica gel, what afforded the pure ester **4f** (18.1 g; 45%; ^{13}C NMR (50MHz, in $CDCl_3$): 19.9, 52.0, 68.1, 71.6, 114.2, 119.1, 126.6, 131.1, 131.6, 133.1, 133.9, 140.8, 152, 163.7, 165.0). *The cyclisation step*: A solution of **4f** (10.6 g, 34.2 mmol) in *o*-dichlorobenzene (1.8 l) was heated for 5 hours at 130°C under argon. Removal of the solvent in a vacuum was followed by flash-chromatography of the pasty residue on silica gel (hexane/AcOEt). The lactone **5c** was eluted first as a solid (Rf 0.64, in 4/1 CH_2Cl_2/AcOEt; the two other isomers have, respectively, Rf 0.56 and 0.48). Recrystallisation from ether gave white crystals (m.p. 94-94.5°C; 6.36g;^{13}C NMR (50MHz, in $CDCl_3$): 18.0, 40.3, 44.5, 47.3, 52.1, 68.7, 70.1, 78.5, 118.9, 126.9, 128.9, 131.4, 153.9, 170.8, 172.6; IR: 1730, 1750, 1780 cm^{-1}).

11- For asymmetric synthesis of a related synthon from lactaldehyde, see: McDougal, P.G.; Jump, J.M.; Rojas, C.; Rico J.G. *Tetrahedron Lett.* **1989**, *30*, 3897-3900.

12- a) Deol, B.S.; Ridley, D.D.; Simpson, G.W. *Aust. J. Chem.* **1976**, 2461-2467; b) Kitahara, T.; Hurata, H. and Mori, K. *Tetrahedron* **1988**, *44*, 4339-4349.

13- Selected ^{13}C NMR data (50MHz, in $CDCl_3$): *(-)*-**8a**: 18.0, 24.7, 30.7, 44.0, 44.2, 47.1, 51.9, 70.9, 80.8, 171.6, 174.0; **2a**: 18.1, 24.9, 39.7, 47.2, 47.4, 52.4, 56.9, 80.2, 167.8, 172.8, 202.0. $[\alpha]_D$ values in ethanol, c=1.

(*Received in France* 16 *March* 1994; *accepted* 12 *April* 1994)