Tetrahedron Letters, Vol. 34, No. 46, pp. 7455-7458, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Highly Efficient Approach to (+)-Grandisol via a Diastereoselective [2+2] Photocycloaddition to 2(5*H*)-Furanones

Ramón Alibés, José L. Bourdelande, Josep Font*

Unitat de Química Orgànica, Departament de Química, Universitat Autònoma de Barcelona, Bellaterra, 08193 Barcelona, Spain.

Abstract: A new approach to (+) and (-)-grandisol is described through a diastereoselective photocycloaddition of ethylene to an easily available homochiral butenolide. Optically pure intermediates are obtained.

(+)-Grandisol is the most important component in the sexual attracting pheromone of the Boll weevil (*Anthonomous grandis*), which is a dangerous insect for the cotton plants.[1]

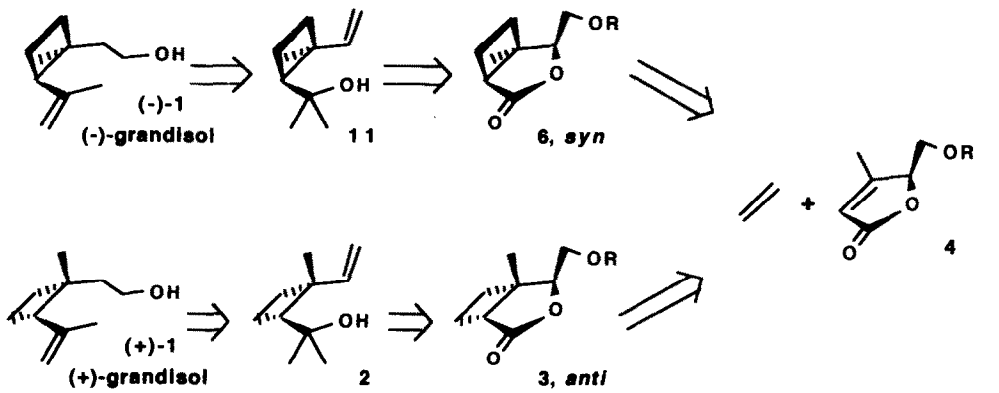
Many syntheses of this monoterpene in its racemic form have been described to date, although the overall yields are not too high.[2] Recently, yields of ≈20% have been claimed in some asymmetric approaches.[3,4] Only two of them are short (less than 10 steps) and show e.e. = 91-100%.[4]

We wish to report here the synthesis of the immediate precursors of (+) and (-)-grandisol following a short and efficient approach that uses an easily available homochiral butenolide as starting material; that ensures the creation of new chiral centers by internal asymmetric induction of the original and sacrificial stereogenic center.

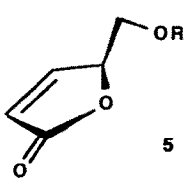
The key intermediate or immediate precursor for the synthesis of (+)-grandisol, (+)-**1**, is the cyclobutane derivative **2**, that has already been transformed into **1**.[4b,5] We related this intermediate with the cyclobutanic lactone **3** (Scheme I) that could be obtained by a stereoselective [2+2] cycloaddition of ethylene to an homochiral α,β-butenolide like **4**; therefore our synthetic approach depends on the asymmetric induction performed by the stereogenic center present in **4**.

We have previously shown that diastereoselection on [2+2] cycloadditions to homochiral 2(5*H*)-furanones depends mostly on the steric effects exerted by the volume of the group R present in the 5 position of the furanone.[6] Diastereomeric excesses of up to 64% were formed in the reaction of **5** with tetramethylethylene. These d.e. were worse than the ones found in Diels-Alder reactions with similar α,β-butenolides,[7] indicating once more the high steric requirements at the transition state of the truly concerted Diels-Alder reaction.

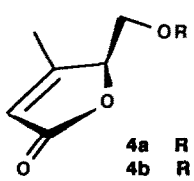
SCHEME I



In spite of these results we undertook the synthesis of (+)-grandisol as planned. (*S*)-5-hydroxymethyl-2(*5H*)-furanone (**5**, R=H)[8] was transformed into its acetate and pivalate derivatives on reaction with Ac_2O and pivaloyl chloride, respectively. Both esters were methylated to the (*S*)-4-methyl-5-hydroxymethyl-2(*5H*)-furanone esters **4a** and **4b** via thermolysis (refluxing dioxane) of the pyrazolines obtained by reaction with diazomethane. The acetate and the pivalate esters **4a** and **4b** were each irradiated (Philips HPK 125W/Acetone/-45°C) in the presence of a saturated atmosphere of ethylene yielding two diastereomers, **3a** and **6a** (as well as **3b** and **6b**) (Table I, Scheme I) with an almost quantitative yield in the second case. It is worth to comment on the influence of the vinylic methyl group that diminishes the face diastereoselectivity in these [2+2] cycloadditions (compare with the results obtained in prior studies[6] with other homochiral butenolides). Although the d.e. are not too high, in the case of the pivalate a simple flash column chromatography gives excellent separation of the two diastereoisomers, thereby giving rise to a short efficient and cheap way to both cyclobutanic intermediates **3b** and **6b** for (+) and (-)-grandisol. The relative configuration of the cycloadduts was determined from their 100 MHz ^{13}C NMR spectra and the major adduct was assigned to an *anti* relationship between the CH_2OR group and the cyclobutane ring. The *anti* adduct (α attack), **3b**, shows cyclobutanic configuration centers identical to those in (+)-grandisol, while the *syn* adduct (β attack), **6b**, relates to (-)-grandisol.



5

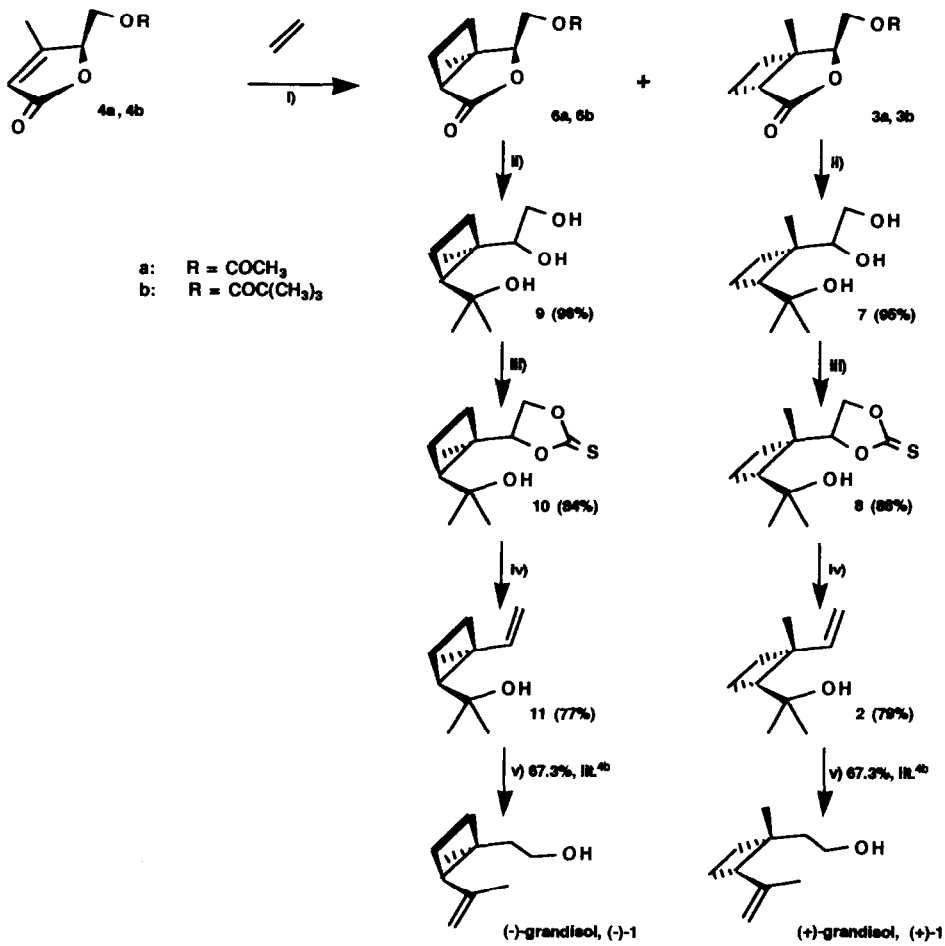


4a R = $COCH_3$
4b R = $COC(CH_3)_3$

TABLE 1: Dependence of the cycloadduct ratio **3:6** (*anti* : *syn*) on the substituents in the γ-position of of the chiral furanone. [a] By *glc*.

furanone	R	d.e. %	yield % **3+6**	cycloadduct ratio *anti* : *syn*
4a	$COCH_3$	6	65	53:47
4b	$COC(CH_3)_3$	24	quantitative[a]	62:38[a]

SCHEME II



i) hv/acetone (HPK-125W); **ii)** MeLi; **iii)** TCDI/THF;
iv) 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine/40°C; **v)** lit.[4b,5]

Lactone **3b** ($\{\alpha\}_D$ -18.53, c:1.32 in $CHCl_3$) opens to the triol **7** ($\{\alpha\}_D$ +2.51, c:1.51 in $CHCl_3$) when an excess of MeLi is added to a THF solution at -78°C. The thionocarbonate **8** ($\{\alpha\}_D$ -62.54, c:1.45 in $CHCl_3$) is obtained from **7** by transesterification with thiocarbonyldiimidazole (TCDI) in THF at 55°C. Finally, **2** ($\{\alpha\}_D$ -34.92, c:1.26 in $CHCl_3$; lit:[2b] $\{\alpha\}_D$ -34.1, c:1.28 in $CHCl_3$) is formed from **8** under mild conditions[9] by stirring with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine at 40°C. In a similar sequence **11** ($\{\alpha\}_D$ +35.24, c:1.30 in $CHCl_3$; lit:[4b] $\{\alpha\}_D$ +33.0, c:0.97 in $CHCl_3$), the immediate precursor of (-)-grandisol, is prepared from the *syn* cycloadduct **6** ($\{\alpha\}_D$ +77.07, c:2.05 in $CHCl_3$) via **9** ($\{\alpha\}_D$ -21.8, c:1.28 in $CHCl_3$) and **10** ($\{\alpha\}_D$ -56.3, c:1.54 in $CHCl_3$). All the diastereoisomers **3-11** are obtained with an optical purity of 100% (by chiral *glc*: Lipodex A, hexakis-(2,3,6-tri-*O*-pentyl)-α-cyclodextrin, 25m x 0.25 mm). The overall yields from **4b** to **2** (the immediate precursor of (+)-grandisol), and **11** (the immediate precursor of (-)-grandisol), are 41% and 24% respectively.

As a conclusion, we describe a new approach to the immediate precursors of both (+)- and (-)-grandisol based in a short and diastereoselective sequence that affords optically pure intermediates and a high yield of such precursors. Since both have been previously converted to (+) and (-)-grandisol our work represents a formal synthesis of the pheromone component of the Boll weevil (*Anthonomous grandis*) and its enantiomer with an equivalent overall yield of 28% for (+)-grandisol and 16% for (-)-grandisol.

ACKNOWLEDGEMENTS

Financial support from DGICYT (Spain) project PB 89-0287 and CIRIT (Generalitat de Catalunya) are gratefully acknowledged.

REFERENCES

1. Tumlinson, J.H.; Hardee, D.D.; Gueldner, R.C.; Thompson, A.C.; Hedin, P.A.; Minyard, J.P.*Science*, **1969**, *166*, 1010.
2. Mori, K.; Fukamatsu, k. *Liebigs Ann. Chem.* **1992**, 489 and references therein.
3. Narasaka, K.; Kusama, H.; Hayashi, Y. Bull. Chem. Soc. Jpn. **1991**, *64*, 1478.
4. a) Demuth, M.; Palomer, A.; Sluma, H.D.; Dey, A.K.; Krüger, C.; Tsay, Y.H. *Angew. Chem.*, **1986**, *98*, 1093; *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 1117. b) Hoffmann, N.; Scharf, H.D. *Liebigs Ann. Chem.* **1991**, 1273.
5. Tumlinson, J.H.; Gueldner, R.C.; Hardee, D.D.; Thompson, A.C.; Hedin, P.A.; Minyard, J.P. *J. Org. Chem.*, **1971**, *18*, 2616.
6. Alibés, R.; Bourdelande, J.L.; Font, J. *Tetrahedron Asymmetry*, **1991**, *2*, 1391.
7. Ortuño, R.M.; Ballesteros, M.; Corbera, J.; Sánchez-Ferrando, F. and Font, J. *Tetrahedron*, **1988**, *44*, 1711.
8. Prepared from 1,2:5,6-Di-*O*-isopropylidene-D-mannitol: Mann, J.; Partlett, N.K.; Thomas, A. *J.Chem. Research(S)*, **1987**, 369.
9. Corey, E.J.; Hopkins, P.B. *Tetrahedron Letters*, **1982**, *23*,1979.

(Received in UK 6 July 1993; accepted 17 September 1993)