Tetrahedron Letters,Vol.26,No.44,pp 5433-5436,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

BOTRYDIAL SYNTHETIC STUDIES. ASYMMETRIC SYNTHESIS OF QUATERNARY CARBON CENTRES.

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Abstract - The synthesis of optically active **4** has been accomplished by asymmetric formation of cyclic ß-keto esters fully substituted at the α-carbon followed by chemoselective reduction of the ester group. Of the asymmetric reactions examined the Koga procedure proved to be the most selective.

Botrydial (**1**), dihydrobotrydial (**2**), and related metabolites produced by the phytopathogenic fungus, Botrytis cinerea, contain an unusual sesquiterpenoid skeleton.[1,2] To our knowledge, no synthetic efforts directed toward botrydial have been previously reported. Retrosynthetic analysis led to the recognition of **3** and (R)-**4** as synthetic precursors of **1**.

Here we report on several approaches to **4**. The crucial problem was, of course, to generate the quaternary carbon center at C-2 by an asymmetric process.[3] Only very recently, a number of methods were developed which permitted enantioselective elaboration of fully substituted carbon centres in specific cases.[4,5]

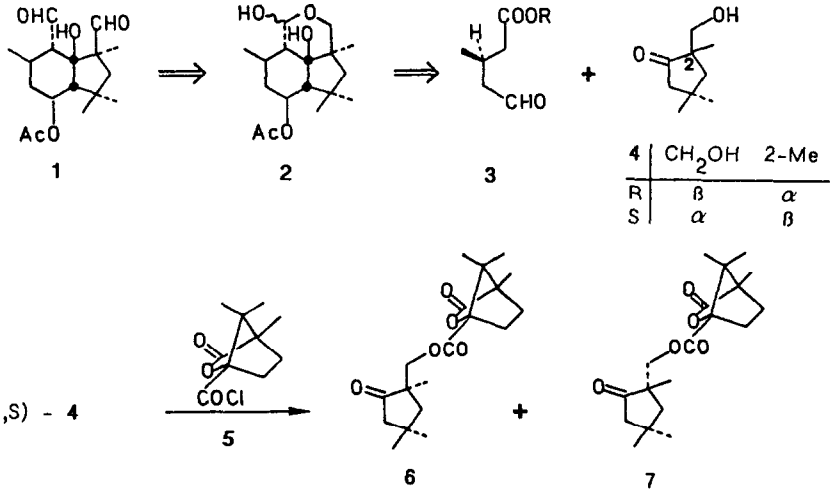
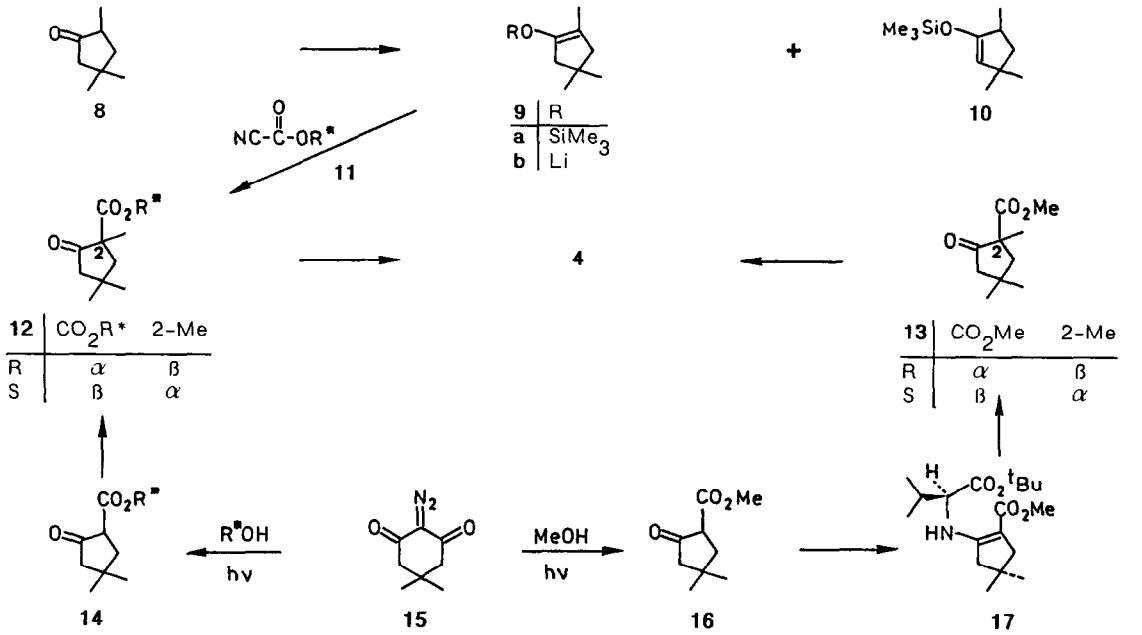
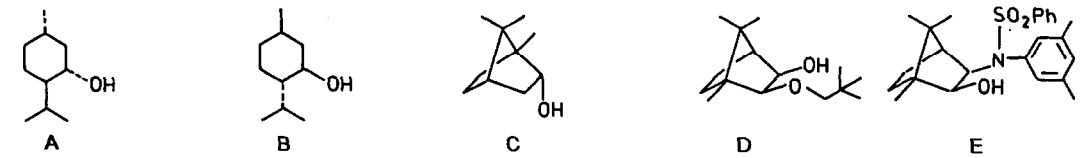


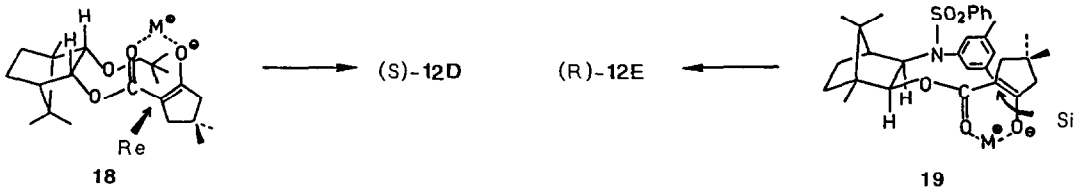
Table 1: Reaction of **9b** with optically active cyanoformates **11**

Cyanoformate	Product	Yield	% d.e. (method of determination)	Configuration of the excess isomer
11A	**12A**	80%	12 (GC)	(S)-**12A**
11C	**12C**	81%	6 (NMR)	not determined
11D	**12D**	70%	14 (GC)	(R)-**12D**



Chiral auxiliaries R*OH:





Racemic **4** was prepared from silyl enol ether **9a** obtained from 2,4,4-trimethylcyclopentanone (**8**)[6] by the classic House procedure[7] (59% yield after distillation, 13:1 mixture of **9a** and **10**) or by Negishi's $KH/BEt_3/ClSiMe_3$ method[8] (85% yield, 8:1 mixture of **9a** and **10**). Reaction of **9a** with paraformaldehyde and Me_3Al in CH_2Cl_2 at 0°C[9] afforded an ene type adduct from which (±)-**4** was obtained by silyl enol ether cleavage (KF in CH_2Cl_2-methanol 1:1) in 93% overall yield. The use of Et_2AlCl[10] led (aqueous work-up) directly to (±)-**4** (87%). The diastereomeric esters of (±)-**4** with (-)camphanic acid (prepared via acid chloride **5**[11]) were readily resolved by medium-pressure chromatography (silica gel, hexane-isopropanol-acetone 25:0.5:0.3). The first eluted ester was shown by single-crystal X-ray analysis to have the undesired (2S)-configuration **7**.[12] (R)-**4** and (S)-**4** were obtained from **6** and **7**, respectively, by base hydrolysis (LiOH, methanol-THF 5:1).[13]

In an attempt to prepare optically active **4** an asymmetric version of Mander's[14] very efficient enolate C-acylation procedure was tried. This method involves reaction of lithium enolates with cyanoformates to provide ß-keto esters in high yield. Optically active cyanoformates **11A**, **11C**, and **11D** were prepared by a) treating (+)-menthol (**A**), (-)-borneol (**C**), and the Oppolzer alcohol **D**[15] with $COCl_2$ in toluene, b) 18-crown-6 catalyzed reaction of the intermediate chloroformates with KCN in CH_2Cl_2.[16] ß-Keto esters **12** were obtained in good yields from **9b** (prepared from **9a** with MeLi[17]) and the cyanoformates using Mander's procedure.[14] The d.e.'s were, however, disappointingly low (see table 1).

We next examined the diastereoselective methylation of ß-keto esters **14B**-**14E**, which were obtained in 70 to 82% yield by photolysis of diazodimedone (**15**) in the presence of optically active alcohols **B** - **E**[18] in THF solution at 0°C (2.5 equiv of **B** - **E**, light source: HPK 125, quartz vessel).[19] The chiral ß-ketoesters were transformed into their respective sodium enolates with NaH and then methylated with excess CH_3I. For experimental conditions, yields, and levels of asymmetric induction, see table 2.

Selective reduction of the ester group in **12A**, **12B**, **12D**, and **12E** to give **4** was achieved by either lithium enolate formation followed by reaction with $LiAlH_4$[20] or by a 3-step procedure involving a) formation of the t-butyldimethylsilyl enol ether, b) reduction with $LiEt_3BH$[21], and c) silyl enol ether cleavage with tetra-n-butylammonium fluoride in THF-water 4:1. The sense of asymmetric induction in the formation of keto esters **12** (see tables 1 and 2) was determined either from the optical rotation of the samples of **4** prepared in these partial reductions or, more reliably, by esterification with **5** and GC comparison with authentic samples of **6** and **7**.[22] The inverse configuration at C-2 in the excess diastereoisomers formed by methylation of ß-keto esters **14D** and **14E**, respectively, can be interpreted in terms of transition states **18** and **19**. It is assumed that a) rotation around the bond between the ester CO and the enolate unit is restricted by cyclic metal ion chelation, and b) that a conformation is preferred in which the ester CO is nearly syn-planar with the alkoxy C-H bond.[23] Although the diastereoselectivity in the methylation of ß-keto esters **14D** and **14E** is only moderate these reactions still provide a rather efficient access to both isomers of **4** since the (2R)- and (2S)-diastereoisomers of **12D** and **12E**, respectively, are readily separated by medium-pressure chromatography.

As an alternative to the above, the applicability of Koga's recently reported diastereoselective alkylation of lithio enamines derived from α-alkyl ß-keto esters was examined.[5] Thus, enamine **17** was prepared from **16** and (S)-valine tert-butyl ester in 67% yield.[24] Lithiation (LDA in toluene), methyl-

Table 2: Methylation of ß-Keto esters **14**

ß-Keto ester	Solvent[25]	Product	Yield	% d.e. (method of determination)	Configuration of the excess isomer
14B	DMF	**12B**	42%	18 (GC)	(R)-**12B**
14C	DMF-toluene (60:40)	**12C**	81%	16 (NMR)	not determined
14D	DMF-toluene (60:40)	**12D**	70%	58 (GC)	(S)-**12D**
14E	THF-HMPA (60:40)	**12E**	60%	62 (HPLC)	(R)-**12E**

ation with CH_3I in the presence of 1 equivalent of HMPA as described by Koga, acid hydrolysis, and chromatographic separation furnished the enantiomeric ß-keto esters **13**. Chemoselective reduction as described above ((i)LDA, (ii) $LiAlH_4$) followed by reaction with **5** provided a 7:93 mixture of **6** and **7** (GC analysis[22]). From this result it can be concluded, that the desired (R)-**4** can be prepared from **16** by either choosing (R)-valine as the chiral auxiliary or (according to Koga's report[5]) by performing the methylation reaction in the presence of THF instead of HMPA.[26]

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12) We thank Prof.Dr.P.Bleckmann (Universität Dortmund) for this determination. Details will be published elsewhere.
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26) Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

(Received in Germany 9 August 1985)