201. [2 + 2] Cycloaddition of Optically Active Ketenes. Synthesis of (−)-Blastmycinone[1])

Preliminary Communication

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[2 + 2] Cycloaddition of (menthyloxy)methylketene (**2**) to *cis*-ethyl propenyl ether showed a *ca.* 3:1 diastereoselectivity. A two-step transformation of the thermodynamically more stable adduct **4** furnished the (2*R**,3*R**)-compound **5** with *ca.* 50% e.e. *(Scheme 1)*. The analogous reaction sequence with *cis*-benzyl 1-hexenyl ether (**9**) and **2** showed a *ca.* 5:1 diastereoselectivity in **10** and **11** *(Scheme 2)*. Absolute configuration of C(3) and C(4) in **11** has been proved by converting it to (−)-blastmycinone. Accordingly, the preferred transition state has been deduced as **15**.

Introduction. – There is still a general interest in synthetic methods to control vicinal stereochemistry, *i.e.* to produce two adjacent chiral centers with a desired configuration. Years ago, we became interested in this problem and found (or was it *vice versa*?) one little stone, *i.e.* a stereoselective α-alkylation of chiral β-hydroxy esters, in this jigsaw puzzle [1]. Later, we turned our attention to the more classical way of stereochemical control, that is to the stereoselective synthesis of small-ring compounds, which can be cleaved to the desired open-chain compound. Thus, bifunctional C_5 units of (*R*,R**)- and (*R*,S**)-configuration were synthesised [2] starting with a [2 + 2]-ketene cycloaddition. Consequently, we searched for means to introduce optical activity into the cyclobutanones formed by ketene additions. At the time we were engaged in the present work, only little was known about optical induction in [2 + 2] cycloadditions in general (for lit., see [3a]), and nearly nothing in ketene cycloaddition. In the meantime, a few relevant publications appeared on this subject. *Ghosez* and coworkers [3] utilised chiral keten-iminium salts with great success, *Wynberg et al.* [4] made use of external chiral bases, and *Green* and *Charbonnier* [5] employed chiral olefins in their study of optical induction in ketene [2 + 2] cycloadditions.

Our approach is based on the attachment of an auxiliary, optically active group at C(2) of the ketene.

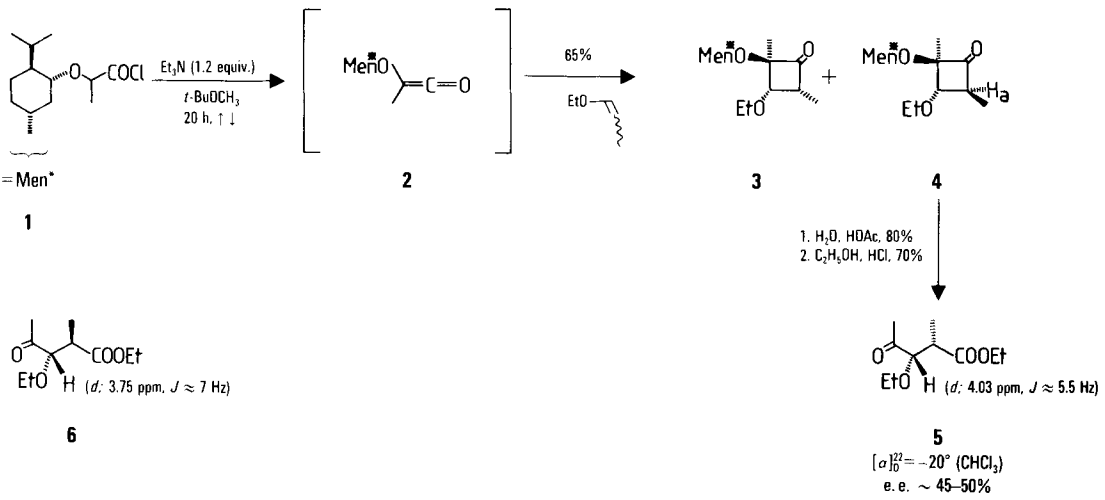
Results and Discussion. – Addition of (menthyloxy)methylketene (**2**), derived from the acyl chloride **1**[2]), to *cis*-ethyl propenyl ether[3]) produced a 1:4 (GLC) mixture (65%) of

[1]) Presented at the 'Swiss Chemical Society Meeting' in Bern, October 1982, at the University of Basel, February 1983 and at the 'XIth Conference on Isoprenoids' in Poland, 1985.

[2]) Acyl chloride **1** was prepared in three steps: reaction on the Na salt of *l*-menthol *(Fluka)* in DMF with ethyl 2-bromopropionate and subsequent hydrolysis (KOH, CH_3OH) furnished 2-(menthyloxy)propionic acid (31%) which was then transformed to **1** ($SOCl_2$, 77%).

[3]) A commercial, *ca.* 4:1 *cis*/*trans*-mixture was used. Under the experimental conditions, only the *cis*-isomer reacted.

Scheme 1



the 3,4-*cis*-cyclobutanone **3** (formed in a kinetically controlled reaction) and the thermodynamically more stable 3,4-*trans*-cyclobutanone **4**[4] (*Scheme 1*). Both compounds were *ca.* 1:3 mixtures of two diastereoisomers as revealed by ^{1}H-NMR (400 MHz; **3**: 4.15, 4.04 (2*d*, J(3,4) ≈ 9.5, *ca.* 1:3 ratio); **4**: 3.79, 3.73 (2*d*, J(3,4) ≈ 7.5, *ca.* 1:3 ratio)). The main product **4** was separated[5]) by flash chromatography (silica gel, hexan/Et_2O 8:2) and converted into the (2*S**,3*S**)-isomer **5**[6]). ^{1}H-NMR analysis of **5** in the presence of a chiral shift reagent confirmed the observation, in the ^{1}H-NMR spectra of **4**, on the diastereoisomers: the signals of H–C(3) and CH_3(5) of **5** showed each a splitting with an integration of *ca.* 1:3, corresponding to *ca.* 50% e.e.[6]).

The same procedure as shown in *Scheme 1* was also applied to (fenchyloxy)-methylketen leading to a *ca.* 1:2 diastereoselectivity. Both the (2*R**,3*R**)-isomer **5** and the (2*R**,3*S**)-isomer **6** were isolated in this experiment. The analogous reaction sequence with (–)-methyl (1*R*,3*S*)-3-methyl-1-indanyloxymethyl keten (for (–)-(1*R*,3*S*)-3-methyl-1-indanol, see [6]) showed no diastereoselection at all. Thus, it was established that there is optical induction in the cycloaddition of (menthyloxy)- and (fenchyloxy)-methyl ketenes to ethyl propenyl ether.

The immediate question was then: which is the preferred transition state, or synonymously, which is the absolute configuration of C(2), C(3), and C(4) in the adducts **3** or **4**? Concerning first the relative configuration at C(2), it is well known [7] [8] that the bulkier substituent of the ketene will be *cis* to the substituent at C(3) in the cyclobutanone after addition to a (*Z*) double bond. We have carried out NOE-^{1}H-NMR experiments with the

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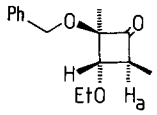
[4]) After 1 h of refluxing, the **3**/**4** ratio was *ca.* 9, after 5 h *ca.* 1.

[5]) Complete separation of **3** and **4** could be achieved. Careful control, also with ^{1}H-NMR, was taken to avoid discrimination of diastereoisomers.

[6]) The formulas in *Scheme 1* are presented in the assumed absolute configuration as deduced for the main product in analogy to the results in *Scheme 2 (vide infra)*.



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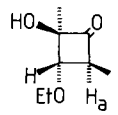

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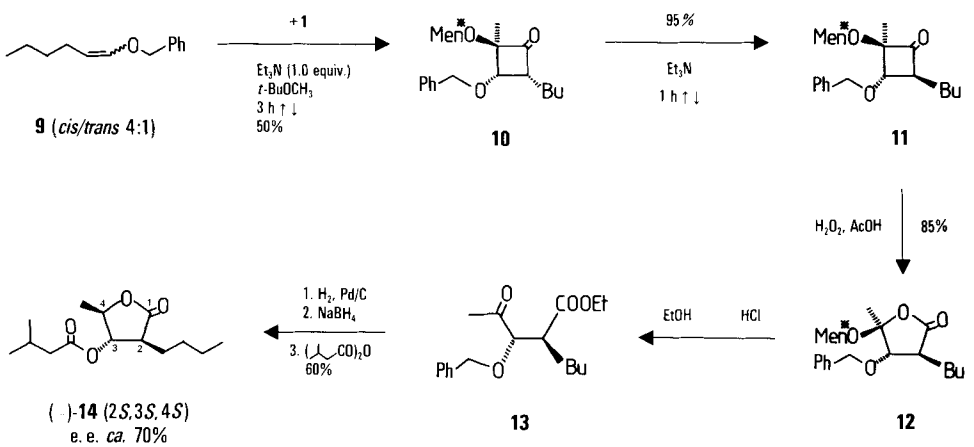
addition products **4**, **7**, and **8**[7]), in order to confirm the relative bulkiness of the CH_3 group in our specially substituted ketenes. In all three cases, irradiation of CH_3–C(2) gave rise to a NOE effect on H_a: 12% in **4**, 10% in **7**, and 16% in **8**. Thus, in all three cases the CH_3 group is bulkier than the alkoxy group.

After having established the relative configuration at C(2) with regard to C(3) and C(4) in **4**, we were interested in the question of the absolute configuration of **5**. For this purpose, we synthesised blastmycinone (**14**) [9] which recently became quite popular in literature [10]. Our synthesis of **14** *(Scheme 2)* is in close analogy to the procedure described in *Scheme 1*. [2 + 2] Cycloaddition of **2** to *cis*-benzyl 1-hexenyl ether[8]) (**9**) furnished the kinetically controlled primary product **10** [^{1}H-NMR: 4.19, 4.21 (2*d*, J(3,4) ≈ 10, ratio *ca.* 1:5, H–C(3))]. The intermediate **10** was converted into the thermodynamic mixture **11**/**10**, ratio 9:1, by refluxing in Et_3N [^{1}H-NMR (400 MHz, $CDCl_3$) of **11**: 3.99, 3.925 (2*d*, J(3,4) ≈ 7.5 Hz, ratio 1:5, H–C(3))]. *Baeyer-Villiger* oxidation of pure **11** (→**12**), followed by treatment with HCl/EtOH led to **13**, which was diastereoisomerically pure and for which the ^{1}H-NMR analysis in the presence of a chiral shift reagent showed a *ca.* 65% e.e. Hydrogenolytic removal of the benzyl group, followed by the reduction of the α-hydroxy ketone with $NaBH_4$ in *t*-BuOH gave a 4:1 ratio of the desired hydroxy lactone and its 4-epimer. This mixture was esterified with isovaleric anhydride and the esters separated on silica gel. The main product (–)-**14** (60% yield with

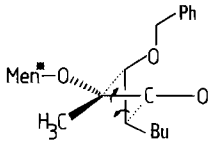
Scheme 2



[7]) For the sake of clarity: **4** and **7** are the thermodynamically more stable 3,4-*trans*-compounds, obtained after base-catalysed epimerisation at C(4) of the kinetically controlled 3,4-*cis*-compound. Compound **8** is the hydrogenation product of the adduct of methyl (3-methyl-1-indanyloxy)ketene to ethyl propenyl ether (see above).

[8]) A 4:1 *cis*/*trans*-mixture was used, prepared in analogy to the product in [11].

respect to **13**) had $[\alpha]_D^{22} = -7.1°$ ($CHCl_3$, $c = 1.2$) which corresponds to an optical purity of 64 or 71% depending on the data given for the natural product ([10a] [10b]: $[\alpha]_D = +11.5°$; [9a]: $[\alpha]_D = +10°$). Both values of e.e. are within the accuracy of the ^{1}H-NMR observations on the diastereoselectivity in **10** and **11** and of the ^{1}H-NMR analysis of **13** in the presence of a chiral reagent (assuming that p = e.e.). Our sample of (−)-blastmycinone ((−)-**14**) had NMR and IR spectra identical with those of the natural compound [9d].



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Based on the known absolute configuration [9a] of natural (+)-blastmycinone, we deduce the absolute configuration of the primary [2 + 2]-adduct **10** as (3*S*,4*R*). Together with the known relative configuration at C(2), this information leads to **15** as the preferred transition state ($\Delta\Delta G^{\neq} \sim 1$ kcal/mol) (see *Footnote 6*).

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