two quenching mechanisms (i.e., only one term in the summation for k_{NR}') where

$$\alpha = 1.4 \times 10^{10}\ s^{-1} \qquad A = 5.4\ kcal/mol$$

$$\beta = 2.3 \times 10^{7}\ s^{-1} \qquad B = 0.95\ kcal/mol$$

The mechanism, which starts to influence the quenching only above 220 K, is assigned to photodimerization. The value obtained for the activation energy of photodimerization (A = 5.4 kcal/mol) is similar to those reported for other photocycloadditions shown to proceed via an exciplex.[2g,12] Using the rate parameters determined here,[7b] we calculate that at 293 K $\phi_D = 0.08 \pm 0.02$, which is compatible with the independent value found by direct measurement.

Registry No. 9-CNA, 1210-12-4; 9-MeOA, 2395-96-2.

(11) The experimental uncertainty is estimated to be 5% for activation energies and 20% for the preexponential factors.
(12) Caldwell, R. A.; Creed, D. *J. Am. Chem. Soc.* **1978**, *100*, 2905-2907, **1979**, *101*, 6960-6965.

New Synthetic Route to (1*R*)-*trans*-Chrysanthemic Ester and to the (1*R*)-*cis*-*gem*-Dibromovinyl Analogue from a Common Intermediate

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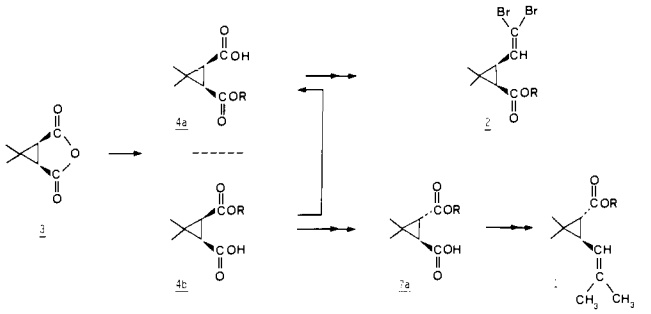
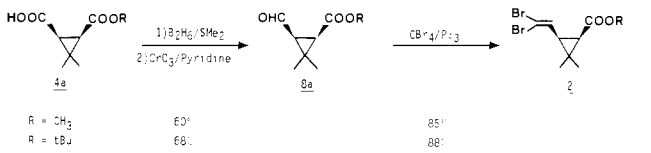
Suitable esters of the (1*R*)-*trans*-chrysanthemic acid (**1**) and its dihalogeno (1*R*)-cis analogue **2** are potent insecticides,[1] safe to mammals,[1] and biodegradable.[1] The higher photostability of **2** (half-life 10 days instead of 5 h for **1**) has opened an important market in agriculture for pest control, especially in fruits, vegetables, and cotton crops, the natural derivative **1** being mainly used for its knock-down effect.[1] A total of 3000 tons of **1** and **2** was manufactured in 1979 and increased production (up to 10000 tons/year) is expected in the near future.[2] We report here on a new synthetic approach[3] that allows the preparation of the most active[1] optical isomers **1** and **2** from the chiral cis monoester of caronic acid **4** (R = CH_3), which is derived from the prochiral caronic anhydride **3** by methanolysis (1 equiv) of CH_3ONa/CH_3OH, 0 °C, 0.1 h, then 10% aqueous HCl)[4] and resolution with optically active α-methylbenzylamine.[5] The proposed methodology not only allows the completely stereoselective interconversion of the two cis-intermediates **4a** and **4b** but also provides simple and stereoselective access to each enantiomer of the trans-series **7a** and **7b**. It completely utilizes the racemate **4**, which can be transformed as desired to one and only one of the four isomers **4a**, **4b**, **7a**, and **7b** and thus to the desired chrysanthemic esters **1** or **2** (Scheme I).

Typically the (1*R*,3*S*)-enantiomer **4a** (R = CH_3) was isolated in pure form as its ammonium salt (mp 143 °C, orthorhombic crystals) in 25% yield (not optimized) after reaction of the racemate **4** (R = CH_3) with (+)-α-methylbenzylamine in acetone and selective precipitation from the same solvent (0.23 M solution, 20 °C, 24 h).

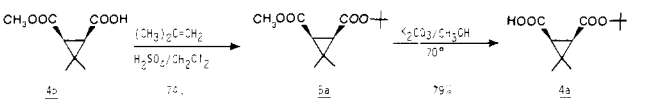
Scheme I



Scheme II



Scheme III



The enantiomer **4b** (R = CH_3) was also isolated as its ammonium salt (mp 139 °C, monoclinic) in pure form in 25% yield (not optimized) on reaction of the material left in the filtrate (after destruction of the remaining ammonium salt) with (−)-α-methylbenzylamine,[5] applying a workup identical with the one used for **4a** (R = CH_3).

The recovery of **4a** and **4b** from their respective ammonium salt was best achieved by treatment with an aqueous potassium carbonate solution (0.5 M, 2 equiv, 20 °C, 0.1 h) followed by careful acidification [HCl, 10%, 1.01 equiv (titration)] and rapid extraction from the acidic medium, which was found to rapidly racemize the product. Under these conditions **4a** and **4b** were each quantitatively isolated in 98% enantiomeric excess.[6a]

The **4a** isomer was directly transformed (Scheme II) to the exceedingly active insecticide **2** by using a set of reactions that we already described on the racemate[4,7] and that proved to be completely stereoselective on the pure enantiomer (Scheme II, R = CH_3).

The "wrong" enantiomer **4b** (R = CH_3) has also been utilized to produce stereoselectively, as desired, **4a** (R = *t*-Bu) or the trans isomer **7a** (R = *t*-Bu), respectively, precursors of **2** (Scheme II) or of the natural chrysanthemic acid.[1,4]

The stereoselective isomerization of the hemicaronic ester **4b** to **4a** (Scheme I), which formally requires a double inversion at the C_1 and C_3 carbons of the cyclopropane ring, was in fact achieved by using the rather simple observation that interconversion of the ester and acid groups on the cyclopropyl ring will give the same result.

This was effectively achieved as follows (Scheme III): the monomethyl ester **4b** (R = CH_3) was readily transformed to the optically active mixed (1*R*,3*S*)-*tert*-butyl methyl diester **5a** (isobutene, trace of H_2SO_4 in CH_2Cl_2, 20 °C) isolated in 74% yield (enantiomeric excess 99.6%),[4b] which contains two ester groups different in both nature (for optical reasons) and reactivity. We took advantage of these differences to achieve the selective hydrolysis[8] of the methyl ester [K_2CO_3 (5 equiv), MeOH/H_2O

(1) M. Elliott and N. F. Janes, *Chem. Soc. Rev.*, **7**, 473 (1978).
(2) We thank Dr. Punja, ICI (PPD) Jealott's Hills Research Station, for valuable discussions, during the sabbatical leave of A.K.
(3) D. Arlt, M. Jautelat, and R. Lantzsch, *Angew. Chem., Int. Ed. Engl.* **20**, 703 (1981).
(4) M. J. Devos, J. N. Denis, and A. Krief, *Tetrahedron Lett.*, 1847 (1978).
(5) (+)-α-Methylbenzylamine, α^{20}_D +39° (neat) (Aldrich); (−)-α-methylbenzylamine, α^{20}_D −39° (neat) Aldrich).
(6) Comparison has been made with authentic samples prepared from pure (1*R*,3*S*) chrysanthemic acid, kindly provided by Roussel Uclaf Co. (Romainville, France). A full account of this work will appear in the full paper. (a) **4a** (R = CH_3), α^{20}_D +29.95° (wet ethanol); (b) **5a** (R = *t*-Bu), α^{20}_D −32.91 (acetone); (c) **4a** (R = *t*-Bu), α^{20}_D +1.78 (wet ethanol).
(7) F. Ramirez and N. McKelvie, *J. Am. Chem. Soc.*, **84**, 174 (1962).
(8) The use of KOH instead of K_2CO_3 (1 equiv KOH, MeOH, reflux) completely epemerizes the product.

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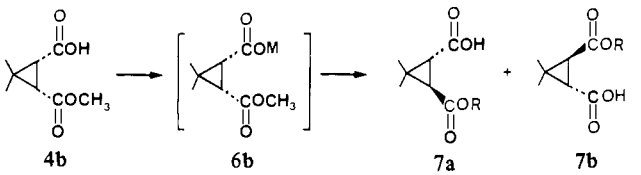
Scheme IV



4b 6b 7a 7b

		yield	7a	7b	ee[a]
entry a	4 equiv of *t*-BuOK/ C_6H_6, 70 °C, 1 h	44% (*R* = *t*-Bu)	73%	27%	46%
entry b	4 equiv of *t*-BuOK/ THF, 70 °C, 1 h	57% (*R* = *t*-Bu)	88%	12%	76%
entry c	4 equiv of KH/THF, 70 °C, 1 h	74% (*R* = Me)	87%	13%	74%
entry d	1 equiv of LiH/3 equiv of *t*-BuOK/THF, 70 °C, 1 h	76% (*R* = *t*-Bu)	98%	2%	96%

[a] ee = enantiomeric excess.

(1:1), 1.3 M solution, 70 °C, 15 h, and then careful acidification to pH 2 with 10% HCl, which produces the desired (1*R*,3*S*)-ester **4a** (R = *tert*-Butyl) (enantiomeric excess 99.6%) in 79% isolated yield.

The transformation of the cis-derivative **4b** (R = CH_3) to the trans-ester **7a** requires the selective epimerization at the ester group. We first tried on **4b** the reaction of *t*-BuOK (4 equiv., benzene or THF, 70 °C, 1 h) under conditions already successfully used by Julia[9] for the isomerization of the cis methyl chrysanthemate to its trans *tert*-butyl analogue. The combined yields of **7** (R = tBu) were modest (44% and 57%, respectively), but the optical purity of the compound was quite low (46% and 76% ee, respectively) (Scheme IV, entries a–b).

After several unsuccessful attempts (Scheme IV, entries a–c), we discovered that the potassium salt of the methyl hemicaronate **6b** (R = CH_3; M = K) quantitatively prepared on reaction of the corresponding acid **4b** (R = CH_3) with potassium hydride (1 equiv/THF) racemizes on heating at 70 °C for 1 h in the same solvent (after acidic hydrolysis, 96% recovery of **4**, **4b**/**4a** = 90:10). Such racemization probably occurs by an internal displacement of the methoxy group, which leads to the intermediate formation of the symmetrical anhydride **3**.

So that such side reaction could be avoided, a protecting group of the acid moiety was required. It must prevent the formation of the potassium salt **6b** (R = CH_3; M = K), must not acidify the hydrogen α to this carbonyl group, and must be cheap.

Lithium was found to be the best candidate since it satisfies the last two requirements and since the lithium salt **6b** (R = CH_3; M = Li) (from **4b** and LiH in THF) does not racemize on heating for 1 h (after acidic hydrolysis, 96% recovery of **4**, **4b**/**4a** = 97:3). Unfortunately, however, this salt does not isomerize to the trans derivative in the presence of an excess of LiH. Addition of some *tert*-butyl alcohol favors the last reaction; it does not, however allow the complete isomerization.

The desired transformation [**4b** (R = CH_3) to **7a** (R = *t*-Bu)] was finally stereoselectively achieved in 76% overall yield and 96% enantiomeric excess by the combination of the two observations just reported. Methyl hemicaronate **4b** was transformed to its lithium salt (1 equiv LiH/THF, 20 °C), potassium *tert*-butoxide (3 equiv, final concentration of **4b** = 0.2 M) was then added, and the solution was heated at 70°C for 1 h prior acidic hydrolysis (Scheme IV, entry d).

In the pyrethroid field only one synthetic strategy involving the separation of the two enantiomers and the recycling of the undesired one has been so far described.[10] Our method compares well with this industrial process since the separation of the enantiomers is accomplished at an early stage of the synthesis, no carbons are wasted, and the more economically valuable cis isomer is produced directly.

Registry No. 1 (R = H), 4638-92-0; **2** (R = H), 53179-78-5; **3**, 67911-21-1; **4a** (R = CH_3), 81873-49-6; (±)-**4** (R = CH_3), 81831-72-3; **4a** (R = CH_3) (+)-α-methylbenzylamine salt, 81938-54-7; **4a** (R = *t*-Bu), 81873-50-9; **4b** (R = CH_3), 81873-51-0; **4b** (R = CH_3) (−)-α-methylbenzylamine salt, 81938-55-8; **5a** (R = *t*-Bu), 81831-73-4; **6b** (M = K), 81938-56-9; **6b** (M = Li), 81938-57-0; **7a** (R = *t*-Bu), 81873-52-1; **7b** (R = CH_3), 27335-36-0; **7b** (R = *t*-Bu), 81873-53-2; **7b** (R = CH_3), 81938-58-1; **8a** (R = CH_3), 55701-02-5; **8a** (R = *t*-Bu), 56194-29-7; **2** (R = CH_3), 61775-87-9; **2** (R = *t*-Bu), 56194-58-2.

(9) S. Julia, M. Julia, and G. Linstrumelle, *Bull. Soc. Chim. Fr.*, 3499 (1966).

(10) (a) J. Martel, German Patent, 1, 935, 386; *Chem. Abstr.*, **72**, 100136d (1970); J. Martel, German Patent, 1, 935, 320; *Chem. Abstr.*, **72**, 121078b (1970). (b) J. Martel and J. Buendia, German Patent, 2, 010182; *Chem. Abstr.*, **73**, 109363c (1970).

Synthesis and Rapid Hydrolysis of a 12-Membered Macrocyclic Peptide Thiolactone

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A macrocyclic thiolactone is common to the metastable binding sites of three serum proteins, the protease inhibitor α_2-macroglobulin[1,2] and the complement components C3[3] and C4.[4] The thiolactone ring is assembled from a five-residue linear segment (**1**, Scheme I) common to polypeptide precursors of each of these proteins. In principle, the thiolactone could exist as either a 12-membered ring (**2**) or a 15-membered ring (**3**). These macrocyclic structures would result from formation of a thiolester linkage between the thiol group of the cysteine residue and the side-chain carboxyl group of the first or second glutamic acid residue, respectively. The data[1–4] are consistent with each of these proteins having partial structure **3** but not **2**.

Recently we described[5] the synthesis of several hexapeptides containing the 15-membered thiolactone ring present in structure **3**. This paper reports the synthesis, characterization, and rapid hydrolysis of hexapeptide **9** (Scheme II), which contains the novel 12-membered thiolactone ring of structure **2**. The 1-thia-5,8-diazacyclododecane ring contains two amide bonds, one thiolester bond, and two chiral centers (3*R*, 9*S*; Cys and Glu in the L configuration).

Macrocyclic peptide thiolactone **9** was assembled from glycine and four L-amino acids by the following strategy. The tripeptide acid **4** was obtained by mixed anhydride coupling[6] of Boc–Cys (4-CH_3Bzl) with Gly–OCH_3 (87% yield), acidolysis[7] of the *tert*-butyloxycarbonyl (Boc) group, mixed anhydride coupling[6] of CH_3CO–Gly to the resulting Cys(4-CH_3Bzl)–Gly–OCH_3 (82% yield), and saponification[8] of the methyl ester (72% yield). The tripeptide amine **5** was prepared by coupling[9] of Boc–Gln 4-

(1) Sottrup-Jensen, L.; Petersen, T. E.; Magnusson, S. *FEBS Lett.* **1980**, *121*, 275–279.
(2) Howard, J. B. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 2235–2239.
(3) Tack, B. F.; Harrison, R. A.; Janatova, J.; Thomas, M. L.; Prahl, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 5764–5768.
(4) Harrison, R. A.; Thomas, M. L.; Tack, B. F. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78* 7388–7392.
(5) Khan, S. A.; Erickson, B. W. *J. Am. Chem. Soc.* **1981**, *103*, 7374–7376.
(6) The mixed anhydride was formed by reaction of the N-acylpeptide acid with *N*-methylmorpholine and isobutyl chloroformate in THF for 5 min at −15 °C. After addition of the amino component, the mixture was stirred for 0.5 h at −15 °C and for 2–20 h at 25 °C.
(7) Treatment with 1:1 (v/v) trifluoroacetic acid/dichloromethane for 0.5 h at 25 °C gave quantitative cleavage of the Boc group.
(8) The methyl ester was hydrolyzed by treatment with 0.1 M NaOH (1.1 equiv) in 9:1 (v/v) methanol/water for 3 h at 25 °C.
(9) Coupling[10] was carried out in DMF in the presence of 1-hydroxybenzotriazole (HOBt; 1.0 equiv) for 0.5 h at 25 °C.
(10) König, W.; Geiger, R. *Chem. Ber.* **1973**, *106*, 3626–3635.

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