of 10 mL of water and 50 mL of 1,2-dimethoxyethan and refluxed for 12 h. After cooling, this solution was poured into a two-phase mixture of pentane (100 mL) and water (50 mL) to precipitate the toluenesulfonamide. This was filtered off and washed with pentane. The pentane layers were dried, the solvent was distilled off, and the allyl benzene (**1a** + the $C_6H_5CHDCH{=}CH_2$ derivative) was isolated by distillation in vacuo.

To gain a better precision in the determination of the isotopic composition by ^2H NMR experiments, we used the 4-deuteriophenyl derivatives **1b** and **3a** and measured the relative signal intensities of the D atom resonances **1a**/**1b** or **3a**/**3b**, respectively.

Acknowledgment. This work has been stimulated by discussions with the late Harold Kwart. We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support and grants.

Registry No. 1, 300-57-2; **1b**, 99532-28-2; **1c**, 99532-29-3; **2**, 4104-47-6; **3**, 1194-56-5; **3a**, 99532-33-9; **3b**, 99532-34-0; **4a**, 99532-23-7; **4b**, 13707-44-3; **5**, 1423-13-8; **6**, 4233-33-4; **7a**, 99532-24-8; **7b**, 99532-25-9; **7c**, 99532-27-1; **7d**, 99532-26-0; D_2, 7782-39-0; allyl bromide, 106-95-6; 1-bromo-4-deuteriobenzene, 13122-33-3; malonic acid, 141-82-2; methyltriphenylphosphonium bromide, 1779-49-3; 1-indanone-2,2-d_2, 10036-02-9; methyl-d_3-triphenylphosphonium bromide, 1787-44-6; 4-deuteriobenzaldehyde, 33836-85-0; 4-deuteriocinnamic acid, 99532-30-6; 4-deuteriohydrocinnamic acid, 99532-31-7; 4-deuteriohydrocinnamic acid chloride, 61233-31-6; 6-deuterioindan-1-one, 99532-32-8.

A Short, Efficient, Highly Selective Synthesis of (1*R*,3*S*)-*cis*-Chrysanthemic Acid through the Microbiological Reduction of 2,2,5,5-Tetramethyl-1,4-cyclohexanedione

Jean d'Angelo* and Gilbert Revial

Unité de Chimie Organique, U.A. du CNRS No. 476, ESPCI, 75231 Paris Cedex 05, France

Robert Azerad* and Didier Buisson

Laboratoire de Chimie et de Biochimie Pharmacologiques et Toxicologiques, U.A. du CNRS No. 400, Université René Descartes, 75270 Paris Cedex 06, France

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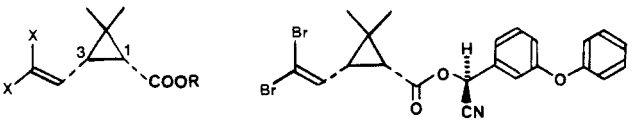
A highly selective synthesis of (1*R*,3*S*)-*cis*-chrysanthemic acid (**1a**), a key intermediate in the industrial preparation of major unnatural pyrethrinoid-type insecticides [deltamethrin (**2**) given as example] is reported. 2,2,5,5-Tetramethyl-1,4-cyclohexanedione (**3**), a key compound in that synthesis, was obtained either by direct tetramethylation of 1,4-cyclohexanedione (**4**) or, in a more efficient manner, by dimethylation of 2,5-dimethyl-1,4-cyclohexanedione (**5**). Microbiological reduction, using various mold strains of dione **3**, afforded enantiomerically pure (*S*)-ketol **11** in 85% yield. This ketol was then transformed into mesylate **12** which was oxidized by means of *m*-chloroperbenzoic acid into the seven-membered ring lactone **16**. Sodium *tert*-amylate promoted transannular cyclization of this lactone was highly selective and gave enantiomerically pure (+)-dihydrochrysanthemolactone **17** (in 70% overall yield, calculated from dione **3**), a direct precursor of acid **1a**.

Chrysanthemic acids, which are cyclopropane ring-containing components of the widely used insecticide pyrethrins, have received much attention in the chemical literature.[1]

It was reported in 1974 by a British group led by M. Elliott that certain unnatural *cis*-chrysanthemic esters **1** (especially their dihalogeno derivatives **1b**) show greater activity and greater photostability than the corresponding trans derivatives[2] (Scheme I). Remarkably, the physiological activity of these pyrethrinoids is closely associated with the 1*R* configuration of the chrysanthemic acid component, the 1*S* enantiomers being many times less effective. For this reason, suitable routes to optically active

Scheme I

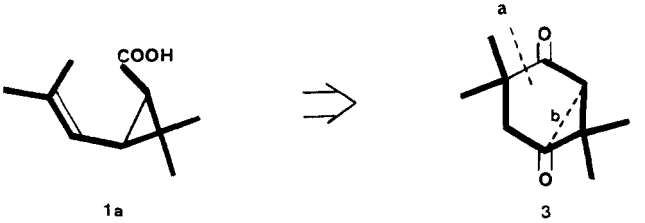


1 2

1a: X = Me, R = H

1b: X = Br or Cl

Scheme II



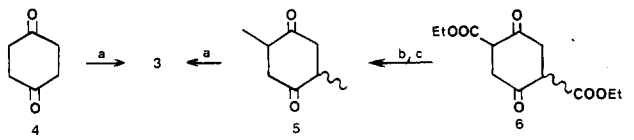
1a 3

(1) For previous syntheses of pyrethrinoic acids, see: (a) Arlt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 703 and references cited therein. (b) Martel, J.; Tessier, J.; Demoute, J. P. Eur. Pat. Appl. 24 241; *Chem. Abstr.* **1981**, *95*, 80711*g*. (c) Kondo, K.; Takashima, J.; Suda, M. U.S. Patent 4237, 058; *Chem. Abstr.* **1981**, *94*, 174447*g*. (d) Schmidt, H. G. *Eur. Pat. Appl.* 31 932; *Chem. Abstr.* **1981**, *95*, 203754*h*. (e) Jakovac, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4659. (f) Lehmkuhl, H.; Mehler, K. *Liebigs Ann. Chem.* **1982**, 2244. (g) Nesmeyanova, D. A.; Rudashevskaya, T. Y.; Dyachenko, A. I.; Savilova, S. F.; Nefedov, O. M. *Synthesis* **1982**, 296. (h) De Vos, M. J.; Krief, A. *J. Am. Chem. Soc.* **1982**, *104*, 4282. (i) Franck-Neumann, M.; Miesch, M. *Tetrahedron Lett.* **1982**, 1409. (j) Franck-Neumann, M.; Martina, D.; Heitz, M. P. *Tetrahedron Lett.* **1982**, 3493. (k) d'Angelo, Ho, Din, Z. U. *Synth. Commun.* **1982**, *12*, 257. (l) d'Angleo, J.; Revial, G. *Tetrahedron Lett.* **1983**, 2103. (m) Mulzer, J.; Kappert, M. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 63. (n) Torii, S.; Inokuchi, T.; Oi, R. *J. Org. Chem.* **1983**, *48*, 1944. (o) Schneider, M.; Engel, N.; Boensmann, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 64. (p) Buisson, D.; Azerad, R.; Revial, G.; d'Angelo, J. *Tetrahedron Lett.* **1984**, 6005. (q) Tessier, J. *Chem. Ind. (London)* **1984**, 199. (r) Mann, J.; Thomas, A. *J. Chem. Soc., Chem. Commun.* **1985**, 737. (s) Cameron, A. G.; Knight, D. W. *Tetrahedron Lett.* **1985**, 3503.

(2) Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A. *Nature (London)* **1974**, *248*, 710.

0022-3263/86/1951-0040$01.50/0

Scheme III[a]



[a] (a) MeI/Na-*t*-AmO; (b) MeI/NaOH; (c) $HClO_4/H_2O$/heat.

esters 1 have been intensively investigated.[3]

The promising aspects of these new pyrethrinoids have precipitated worldwide research activity in this field. Among the derivatives, deltamethrin (**2**) exhibits unusual properties:[4] it is the most effective insecticide known to date (being approximately *100 times* more active than DDT), safe to homeotherm animals (mammals, birds), and easily biodegradable (half-life in soil: ca. 10 days). The exceptional potency of deltamethrin has thus opened up an important market, especially in agriculture for pest control.

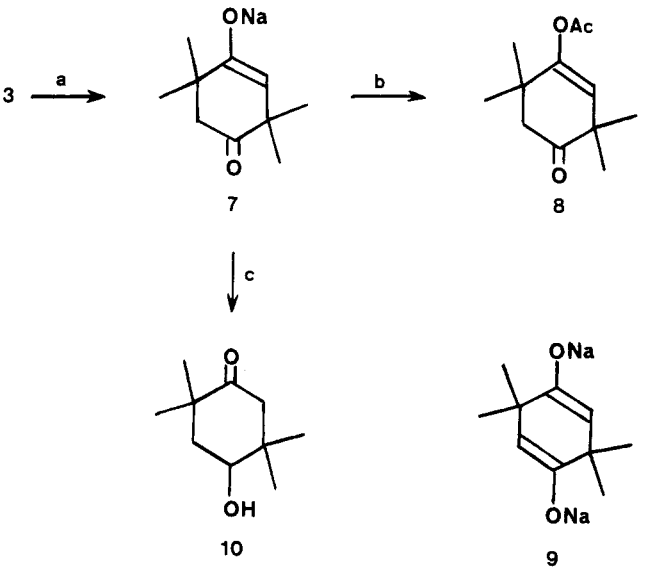
In this paper we wish to report a short, efficient, highly selective synthesis of (1*R*,3*S*)-*cis*-chrysanthemic acid (**1a**), a key intermediate in the industrial preparation of deltamethrin[5].

One of the major difficulties encountered in synthesizing acid **1a** is the stereoselective creation of the cis disubstituted pattern on the cyclopropane ring, since it is disfavored thermodynamically [thus, *cis*-chrysanthemic esters readily isomerize with base into the corresponding trans derivatives[6]]. We reasoned that such a problem (the *diastereoselectivity control*) could be easily solved in creating the cyclopropane ring in a *transannular fashion*, starting from a six- or a seven-membered ring compound; indeed, the fusion of the rings in the resulting strained [3.1.0] and [4.1.0] bicyclic products is necessarily cis.[7]

Our retrosynthetic design for the target molecule **1a** is outlined in Scheme II, wherein the key intermediate is 2,2,5,5-tetramethyl-1,4-cyclohexanedione (**3**). Remarkably, both compounds **1a** and **3** are isomeric ($C_{10}H_{16}O_2$) and their backbones are closely related, as shown in heavy lines in Scheme II; the synthesis (**3** → **1a**) will require, therefore, only two main operations symbolized by dotted lines in formula **3**: viz., a regioselective oxidation of the ring (a) and an intramolecular cyclopropanation step (b). Noteworthy is that both carbonyl groups of dione **3** are needed for such a cyclopropanation process; one of them will be first reduced, and the resulting alcohol then transformed into an appropriate departing group, and the second carbonyl group will be the latent enolate source for the intramolecular nucleophilic displacement of this group.

The synthesis of the key compound **3** has been greatly facilitated by the fact that this molecule is *centrosymmetrical*. We have developed two alternative routes for this purpose (Scheme III).

Scheme IV[a]



[a] (a) Na-*t*-AmO (1 equiv); (b) Ac_2O; (c) DIBAH, then H_2O.

Direct tetramethylation (under "thermodynamic" enolate formation conditions[8]) of 1,4-cyclohexanedione (**4**) led to the expected dione **3** but in moderate yield (ca. 50%): significant amounts of regioisomeric trimethylated and pentamethylated derivatives were formed simultaneously. We reasoned that *dimethylation* of 2,5-dimethyl-1,4-cyclohexanedione (**5**) would be more regioselective than direct tetramethylation of 1,4-cyclohexanedione, since in the former compound the two methyl groups are already in the requisite positions.

This was actually the case, as shown by the following stepwise route. Dimethylation, followed by didecarbethoxylation, of the commercially available diketo diester **6** readily led to 2,5-dimethyl-1,4-cyclohexanedione (**5**) (as a mixture of stereoisomers), which was then dimethylated to dione **3** in an efficient manner (yield ≥80%).

Irrespective of the subsequent synthetic strategy, the next problem we had to solve was the *desymmetrization* of dione **3**. For this purpose, the *chemodifferentiation*,[9] by *monoreduction*, of the two *homotopic*[10] carbonyl groups of this *pro-1 chiral*[10b] dione was investigated, by using either a chemical or an enzymatic method.

The proposed *chemical differentiation* involved the formation of the *monoenolate* of dione **3**. Thus, when this dione was treated under *equilibrating conditions*[8] with 1 equiv of base (sodium *tert*-amylate), monoenolate **7** was the only species formed—as shown by an enolate trapping experiment with acetic anhydride, which afforded exclusively enol acetate **8** (Scheme IV).

We assume that two factors contributed to the success of the monoenolate formation of dione **3**: (i) dienolate **9**,

(3) Enantioselective routes to (1*R*)-*cis*-chrysanthemic acids (conventional racemic mixtures resolution methods are not included). (a) Chemical approach, see ref 1b. (b) Enzymatic approaches, see ref 1e and: Mohr, P.; Waespe-Šarčević, N.; Tamm, C.; Gawronska, K.; Gawronski, J. *Helv. Chim. Acta* **1983**, *66*, 85. Schneider, M.; Engel, N.; Hönicke, P.; Heinemann, G.; Görisch, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 67. (c) Syntheses from the "chiral pool", see ref 1n,r.

(4) "Deltamethrine"; a Roussel-Uclaf Monography, 1982.

(5) For a preliminary report in this field, see ref 1p.

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

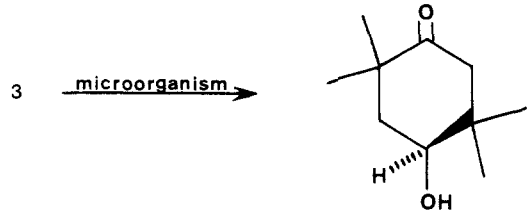
(7) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; p 271. The diastereocontrol in several approaches to *cis*-chrysanthemic acids is based on the use of such strained bicyclic intermediates; see, for example, ref 1b,c, 4, 6, and: Sevrin, M.; Hevesi, L.; Krief, A. *Tetrahedron Lett.* **1976**, 3915.

(8) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979.

(9) In the absence of more appropriate terminology, in this context we use the term *chemodifferentiation* in the following restrictive sense: distinction (by *monoderivatization*) of one of the (n) homomorphic functions in a given molecule. There is so the problem of differentiation of a given function that is present in *two different species* (intermolecular chemodifferentiation): in the present case, namely, the carbonyl function in the starting compound **3** and its derivative **7** (chemical differentiation) and that in the couple diketone **3**–ketol **11** (enzymatic differentiation). It should be remembered that the term chemodifferentiation—as employed in its usual sense—generally refers to the distinction of a given moiety among others of similar reactivity that are present in the *same molecule* (intramolecular chemodifferentiation).[22b]

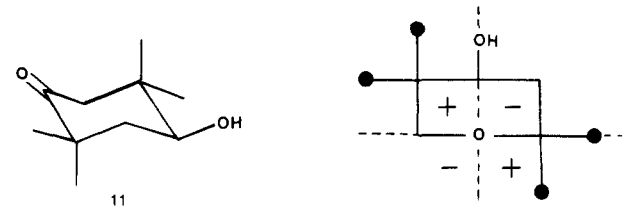
(10) For a discussion of this stereochemical terminology, see: (a) Reference 13a, Chapter VI. (b) Mislow, K.; Siegel, J. *J Am. Chem. Soc.* **1984**, *106*, 3319.

Scheme V



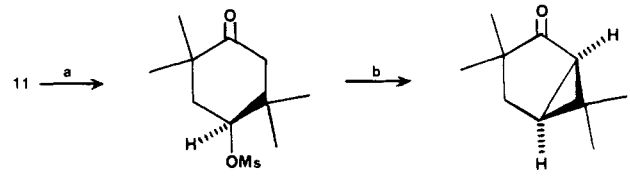
11

Scheme VI



11

Scheme VII[a]



12 13

[a] (a) $MsCl/Et_3N$; (b) Na-*t*-AmO.

a species in possible equilibrium with monoenolate **7**, is disfavored thermodynamically; (ii) the enolate function and the free carbonyl group in monoenolate **7** are both very hindered and thus the possible aldol condensation side reactions were suppressed. The two following experiments strongly supported these last proposals: (i) "*kinetic*" *deprotonation*,[8] using 1 equiv of lithium diisopropylamide (THF, −78 °C) of dione **3**, led to a mixture of starting compound **3** and its mono- and dienolate; (ii) *unhindered* diketone **4**, treated with 1 equiv of base under equilibrating conditions (sodium *tert*-amylate at 0 °C), afforded a complex mixture of condensation products.

Because one of the carbonyl groups in monoenolate **7** is "masked", the in situ reduction of **7** by diisobutylaluminum hydride led, after hydrolysis, to the expected racemic ketol **10** in almost quantitative yield.

Enantioselective reduction of monoenolate **7**, using various chiral (but in principle hindered) reagents, has also been investigated. Regardless of the experimental conditions, none of the expected ketol **10** was formed (for example, using Noyori's reagent[11] no reaction occurred, even at 20 °C), a failure that reflects the considerable hindrance of the ketonic group in compound **7**.

Let us now examine the differentiation of the carbonyl groups of dione **3** by *enzymatic monoreduction*. We expected that such a method should be *highly enantioselective*, thus solving the crucial problem of the control of the first asymmetric center in the present synthesis. Moreover, according to Prelog's rules[12], this enzymatic monoreduction should give mainly *S* ketol **11** (Scheme V), which is precisely the enantiomer required for the synthesis of (1*R*,3*S*)-chrysanthemic acid (**1a**), in light of the presumed mechanism (S_N2) of the cyclopropanation process (vide infra).

The successful stereoselective reduction of open-chain or cyclic pro-1 chiral 1,2-,[13] 1,3-,[14] and 1,4-diketones[15] by enzymatic or microbiological techniques has occasionally been described. In our case, however, three stringent conditions had to be satisfied: (i) the reduction rate had to be largely unaffected by the presence of a hindered tetrasubstituted carbon atom adjacent to the carbonyl group, a situation which is known to reduce dramatically the reactivity of some commonly used dehydrogenases,[13a] (ii) the reduction had to "stop" at the ketol stage, and (iii) the stereoselectivity of the reduction had to be high and to afford the desired *S* ketol **11**.

A screening procedure involving collection strains showed that numerous filamentous molds were able to reduce rapidly the diketone **3**, at 0.5–1 g/L concentrations (Table I). Yeasts were relatively inefficient, except for certain strains. In all cases, the reduction was highly chemoselective, giving mostly the (monoreduced) ketol, and, except for one case (*S. montanus*), highly enantioselective, as revealed by spectroscopic (^1H NMR) and chromatographic data (see Experimental Section). Moreover, that this reduction product was the desired *S* ketol **11** was established by the strongly positive Cotton effect (centered at 290 nm) observed in its CD spectrum, as expected from the octant projection[16] of this molecule [three positive contributions by the methyl groups when in its energetically preferred conformation (by ca. 2.2 kcal/mol),[17] in which the hydroxyl group is equatorial (Scheme VI)].

Two strains (*C. lunata* and *A. ochraceus*) were selected for their high reduction rate and the high optical purity of the product and used for a preparative reduction of diketone **3**. In a study intended to optimize the production of the ketol, it was shown that, provided sufficient glucose was added to the incubation mixture, as much as 15–20 g/L of the dione **3** (solid added in 5 g/L amounts) could be quantitatively reduced over a 2-week period to afford *enantiomerically pure S* ketol **11** in 85% yield.

With the desired *S* ketol **11** in hand, we had next to examine the conversion of this compound to the target molecule **1a**. To achieve this end two strategies were tested, viz., an intramolecular cyclopropanation process

(11) Haubenstock, H. In "Topics in Stereochemistry"; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1983; Vol. 14; pp 231–300.

(12) Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119.

(13) (a) Jones, J. B.; Beck, J. F. In "Applications of Biochemical Systems in Organic Chemistry"; Jones, J. B., Sih, C. J., Perlman, D., Eds.; Wiley: New York, 1976; Part I, pp 236–401. (b) Aklin, W.; Kis, Z.; Prelog, V. *Croat. Chem. Acta* **1965**, *37*, 11. (c) Imuta, M.; Ziffer, H. *J. Org. Chem.* **1978**, *43*, 3319, 3530. (d) Neuberg, C.; Lustig, H.; Cogan, R. N. *Arch. Biochem. Biophys.* **1943**, *1*, 391. (e) Neuberg, C. *Biochem. Biophys. Acta* **1950**, *4*, 170.

(14) Bellet, P.; Nominé, G.; Mathieu, J. *C. R. Seances Acad. Sci., Ser. C* **1966**, *263*, 88. Gibian, H.; Kieslich, K.; Koch, H. G.; Kosmol, H.; Rufer, C.; Schröder, E.; Vössing, R. *Tetrahedron Lett.* **1966**, 2321. Kosmol, H.; Kieslich, K.; Vössing, R.; Koch, H. J.; Pedzoldt, K.; Gibian, H. *Liebigs Ann. Chem.* **1967**, *701*, 199. Bellet, P.; Thuong, T. V. U.S. Patent 3 432 393, 1969. Lee, S. F.; Barth, G.; Kieslich, K.; Djerassi, C. *J. Am. Chem. Soc.* **1978**, *100*, 3965. Schwarz, S.; Truckenbrodt, G.; Meyer, M.; Zepter, R.; Weber, G.; Carl, C.; Wentke, M.; Schick, H.; Welzel, H. P. *J. Prakt. Chem.* **1981**, *323*, 729. Lee, S. F.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1981**, *103*, 295. Brooks, D. W.; Grothaus, P. G.; Irwin, W. L. *J Org. Chem.* **1982**, *47*, 2820; **1983**, *48*, 5413. Lu, Y.; Barth, G.; Kieslich, K.; Strong, P. D.; Duax, W. L.; Djerassi, C. *J. Org. Chem.* **1983**, *48*, 4549. Brooks, D. W.; Mazdiyasni, H.; Chakrabarti, S. *Tetrahedron Lett.* **1984**, 1241.

(15) Prelog, V. In "CIBA Foundation Study Group"; Churchill: London, 1959; No. 2, pp 79–104. Wang, N. Y.; Hsu, C. T.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6538. Lieser, J. K. *Synth. Commun.* **1983**, *13*, 765.

(16) Moffitt, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi, C. *J. Am. Chem. Soc.* **1961**, *83*, 4013.

(17) See ref 7, p 237. Furthermore, the proposed conformational assignment is supported by the ^1H NMR spectrum of this molecule that clearly indicated that proton H-4 is axial (see Experimental Section).

Table I. Reduction of 2,2,5,5-Tetramethyl-1,4-cyclohexanedione (3)[a] by Various Yeast and Fungi Strains

microorganism (strain number)	reacn time h	produced ketol			produced diol,[b] %	recovered dione,[b] %
		yield,[b] %	absol config	ee,[c] %		
Saccharomyces cerevisiae[d]	139	0.4				99.6
S. uvarum (NRRL Y-969)	116	3.0				97.0
S. montanus (CBS 6772)	46	12.6				87.4
	139	48.0	*S* > *R*	1.4		52.0
Kluyveromyces fragilis (NRRL Y-610)	46	2.0				98.0
	139	4.3				95.7
K. dobzanskii[d]	46	1.4				98.6
	137	7.6				92.4
Aspergillus niger[d]	48	66.1	*S*	>98	1.0	32.8
A. ochraceus (ATCC 1008)	72	60.0	*S*	90		40.0
A. ochraceus (ATCC 1009)	46	89.2	*S*	>98	10.8	
Curvularia lunata (NRRL 2380)	46	66.7				33.3
	75	98.2	*S*	>98		1.8
C. lunata (NRRL 2178)	46	87.8			0.7	11.5
	137	97.0	*S*	>98	1.2	1.8
Geotrichum candidum[d]	46	6.7				93.3
	119	31.7	*S*	>98		68.3
G. fragans[d]	46	34.1				65.9
	137	79.5	*S*	96		20.5
Mucor plumbeus[d]	46	98.1	*S*	>98	1.6	0.3
M. racemosus[d]	46	67.7				32.3
	75	85.2	*S*	>98		14.7
Penicillium chrysogenum[d]	75	20.0				80.0
	119	69.9	*S*	>98		30.1
P. verrucosum[d]	28	7.4				92.6
	119	59.1	*S*	95	0.4	40.5
Rhizopus arrhizus (ATCC 11145)	46	10.8				89.2
	120	30.5	*S*	>98		69.5

[a] 1 g/L added in EtOH (20 mL/L). [b] Determined by quantitative VPC analysis on DEGS 10% at 170 °C. [c] Determined by quantitative VPC analysis of the isopropylurethane derivative on a chiral column (see Experimental Section). [d] Local strains obtained from the Laboratoire de Cryptogamie, Université de Paris-Sud, Orsay, France.

followed by a Baeyer–Villiger oxidation and the same two transformations in the opposite order.

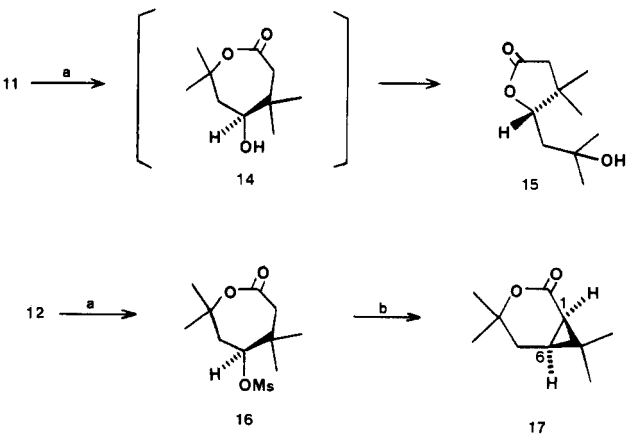
In the *former strategy* (Scheme VII), ketol **11** was first transformed into mesylate **12**. Base-induced cyclization of this mesylate readily led to the expected bicyclic compound **13**, the proposed absolute configuration of which was deduced from the presumed mechanism (S_N2) of the cyclopropanation process. Baeyer–Villiger oxidation of compound **13** was next attempted. Irrespective of the experimental conditions, none of the expected lactone was obtained (ketone **13** was recovered in all cases). Thus the considerably hindered carbonyl group of this molecule appears to be relatively inaccessible to the reagents commonly used for this purpose. In contrast, Julia and coworkers have reported a successful regioselective Beckmann rearrangement of the oxime of this racemic bicyclic ketone.[6]

Pursuing now the *second strategy* (Scheme VIII), ketol **11** was first oxidized by using *m*-chloroperbenzoic acid. Instead of the expected seven-membered ring lactone **14**, the thermodynamically more stable five-membered ring compound **15** was obtained, the result of an intramolecular translactonization process. This difficulty was easily circumvented by oxidizing mesylate **12** rather than ketol **11**. As expected, such an oxidation process was highly regioselective[18] and gave exclusively the seven-membered ring lactone **16**, which was then cyclized with base to produce *enantiomerically pure* 1*R*,6*S* bicyclic lactone **17**. All physical and spectral data of compound **17** (notably its melting point and specific rotation) were in complete agreement with those previously reported for (+)-dihydrochrysanthemolactone.[1n]

The highly selective transformation (**16** → **17**) clearly indicates that (i) as predicted the intramolecular nucleophilic displacement of the mesyl group involved a pure S_N2-type process that established the *S* configuration at center 6, (ii) as it was pointed out in the beginning of this article the ring junction in the fused bicyclic lactone **17** is necessarily cis; consequently the configuration of the newly created asymmetric center (center 1) is *R*. Such a S_N2-type mechanism has previously been proposed for a similar transannular cyclopropanation process in the caryophyllene series.[19]

The above approach to lactone **17** is a formal synthesis of (1*R*,3*S*)-*cis*-chrysanthemic acid **1a**, since the former compound has previously been converted to the latter (quantitatively by heating in pyridine in presence of magnesium bromide).[20]

Scheme VIII[a]



[a] (a) MCPBA; (b) Na-*t*-AmO.

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Several comments should be made concerning this synthesis. According to Quinkert,[21] "one of the main challenges of synthetic chemistry is to find routes that satisfy the demands of industrial applicability to enantiomerically pure compounds with biologically important properties". We believe that our synthesis is excellent in the context of this challenge; indeed, with an overall yield of 70% (calculated from the dione **3**), it is one of the most efficient entries known to date to the optically active *cis*-chrysanthemic acid series.

Furthermore, the above route is highly chemo-, regio-, diastereo-, and enantioselective, satisfying, thus, the main criteria of modern synthetic design.[21,22] In this respect we must note that a microbiological (enzymatic) method has been used to assure the crucial control of the first asymmetric center, and, consequently, the absolute configuration of the final molecule. We anticipate that such a biochemical method, based on the enantiotopic face (or group) differentiation of a pro-1 chiral substrate, will undoubtedly play an increasing role in organic synthesis,[23] particularly in the case of symmetrical compounds (e.g., meso compounds), since such substrates are easily accessible through the conventional chemical routes.

From a practical point of view, this approach is short and uses only common, inexpensive reagents. Furthermore it requires no drastic conditions (most of the reactions are performed at room temperature) and all of the intermediates are crystalline. These, of course, are highly desirable conditions for an industrial synthesis. Likewise, two salient features of the bioreduction step confer an industrial feasibility to the synthesis: (i) the use of an entire microorganism rather than an isolated enzyme with which is more difficult to work (inter alia there is the problem of the regeneration of cofactors) and (ii) the relatively high concentration of the substrate in the fermentation medium.

As a concluding remark, it should be noted that, among the syntheses of the biologically active, industrially important compounds, this is one in which a microbiological step and sophisticated chemical design are effectively integrated.

Experimental Section

General Methods. Melting points were recorded on a Kofler bench or a Fisher-Johns apparatus. ^{1}H NMR spectra (Me_4Si internal standard) were recorded on 60- or 90-MHz Varian or 250- or 400-MHz Brucker spectrometer. IR spectra were recorded on a Perkin-Elmer instrument. Mass spectra were measured on a MS-30 mass spectrometer. Circular dichroism data were measured in a 1-cm silica cell on a Roussel-Jouan dichrograph, made available by the courtesy of Dr. Guschelbauer (C.E.A., Saclay, France). The following workup was generally used: the water-soluble solvents were first removed, and the residue was taken up in ether and water. The organic layers, after drying over magnesium sulfate, were concentrated under reduced pressure, and the residue was chromatographied on silica. The purity of all new compounds was controlled by TLC and/or VPC. The enantiomeric purity of ketol **11** as the corresponding isopropyl urethane derivative[24] was routinely tested by VPC on a Chrompack fused silica column (50 m × 0.25 mm) coated with XE-60–valine–(*S*)-phenylethylamide (carrier gas, helium (1.5 bar); column temperature, 170 °C); the retention times of the *S* and the *R* ketol derivatives were respectively 25.2 and 25.6 min.

2,2,5,5-Tetramethyl-1,4-cyclohexanedione (3). Method A. To a mixture of 4.48 g (40 mmol) of 1,4-cyclohexanedione (**4**) and 10.2 mL of methyl iodide (23.3 g, 165 mmol) in 100 mL of dry THF was added dropwise at 0 °C 106 mL of a 1.5 M solution of sodium *tert*-amylate in benzene (160 mmol). The solution was then stirred for 1 h at 20 °C. The product **3** was obtained in 50% yield as white crystals; mp 112 °C; IR (Nujol) 1700 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 1.1 (s, 12 H), 2.5 (s, 4 H).

Method B. To a mixture of 25.6 g (100 mmol) of diethyl 1,4-cyclohexanedione-2,5-dicarboxylate (**6**) and 10.4 g of sodium hydroxide (260 mmol) in 250 mL of ethanol was added 13.7 mL (31.2 g, 220 mmol) of methyl iodide. The solution was stirred for 4 days at 20 °C. The solvent was removed, and the crude residue was then refluxed in 200 mL of 20% perchloric acid for 2 h. 2,5-dimethyl-1,4-cyclohexanedione (**5**) was obtained in 60% yield as crystals (mixture of stereoisomers; TLC, ^{1}H NMR); IR (Nujol) 1700 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 1.1 (d, 6 H) 2.2–3.0 (m, 6 H).

To a mixture of 3 g (21 mmol) of dione **5** and 2.6 mL (5.9 g, 42 mmol) of methyl iodide in 30 mL of THF was added to 0 °C 28 mL of a 1.5 M solution of sodium *tert*-amylate in benzene (42 mmol). The mixture was then stirred for 15 min at 20 °C. Compound **3** was obtained in 82% yield.

4-Acetoxy-2,2,5,5-tetramethyl-3-cyclohexen-1-one (8). To 353 mg (2.1 mmol) of dione **3** in 2 mL of THF at −40 °C was added 1.5 mL of a 1.4 M solution of sodium *tert*-amylate in benzene (2.1 mmol). The mixture was stirred for 1 h at 0 °C. Acetic anhydride (0.612 mL, 661 mg, 6.5 mmol) was then added at −78 °C, and the resulting mixture was stirred for 30 min at 20 °C. Compound **8** was obtained in 91% yield as an oil: IR (neat) 1755, 1715, 1675 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 1.1 (s, 6 H), 1.2 (s, 6 H), 2.15 (s, 3 H), 2.45 (s, 2 H), 5.1 (s, 1 H).

(*R*,*S*)-4-Hydroxy-2,2,5,5-tetramethylcyclohexan-1-one (10). To 2 g (12 mmol) of dione **3** in 12 mL of THF was added dropwise at −20 °C 8 mL (12 mmol) of a 1.5 M solution of sodium *tert*-amylate in benzene. The mixture was stirred for 1 h at 0 °C. A 1 M solution of diisobutylaluminum hydride in hexane (24 mL, 24 mmol) was then added at −20 °C and the resulting mixture was stirred for 30 min at this temperature. The reaction was then "quenched" by addition of 1 mL of acetone and 1 mL of methanol. Compound **10** was obtained in 90% yield as crystals; mp 84 °C; IR (Nujol) 3420, 1680 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.9 (s, 3 H), 1.05 (s, 3 H), 1.1 (s, 3 H), 1.2 (s, 3 H), 1.7–2.6 (m, 5 H), 3.9 (m, 1 H).

(*S*)-4-Hydroxy-2,2,5,5-tetramethylcyclohexan-1-one (11). Method A (General Screening Procedure). Yeasts and fungi strains, obtained from various collections, were routinely maintained on agar slants containing, in 1 L, glucose (20 g), peptone (5 g), yeast extract (5 g), malt extract (5 g), and Difco Bacto-Agar (20 g). Yeast cells or fungal spore suspensions, obtained by addition of 1–2 mL of saline to freshly grown slants, were used to inoculate 100-mL vials containing 50 mL of a semisynthetic medium.[25] After 2–4 days in a New-Brunswick rotatory shaker (about 150 rpm) at 24 °C, 50 mg of the diketone **3** in 2 mL of ethanol was added and incubation was continued for 2–5 days. Aliquots (1 mL) were periodically removed and extracted with ethyl acetate (0.3 mL). After centrifugation, 1–2 μL of the organic solution was chromatographied on a 10% DEGS column (100 × 0.5 cm) at 170 °C (carrier gas, nitrogen) to estimate the amount of the reduced products (retention times: diketone, 3.6 min; ketol, 10.5 min; diols, 13.6 and 16.5 min). The incubation was stopped by addition of Celite (3 g), filtration, and repeated extraction of the sodium chloride–saturated filtrate with methylene chloride. The organic extract, dried over anhydrous sodium sulfate, was evaporated and an aliquot (1–2 mg) of the dry residue was treated (100 °C; 30 min) in a screw-capped vial with isopropyl isocyanate (150 μL) in methylene chloride (200 μL).[24] Excess reagent and solvent were removed in a stream of dry nitrogen and the derivative, dissolved in methylene chloride (0.5 mL), was analyzed by VPC on the chiral column.

Method B (Preparative Method). A 1-L Erlenmeyer flask containing 500 mL of the usual liquid medium[25] was inoculated with 25 mL of a *Curvularia lunata* (NRRL 2380) preculture in

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the same medium and placed on a rotatory shaker (150 rpm) at 24 °C for 24 h. The crystalline diketone **3** (2.5 g) and ethanol (8 mL) were successively added and the flask shaken again at a moderated rate (100 rpm). Glucose (50%) was added after 3 (20 mL) and 9 days (10 mL). When all of the initial diketone was consumed (6 days), another 2.5-g amount was added. After 13 days (98% reduction by VPC; no diol detected) the incubation was stopped by addition of Celite (40 g), filtration, and repeated extraction of the sodium chloride–saturated filtrate with methylene chloride. The organic solution, dried over anhydrous sodium sulfate, was evaporated, and the residue was crystallized from methylene chloride–hexane to give 4.1 g (82%) of ketol (**11**): mp 103–104 °C; $[\alpha]^{20}_D$ +89.7° (*c* 0.3, MeOH); CD (0.65 mg/mL in MeOH) positive Cotton effect centered at 290 nm ($\Delta\epsilon c$ 6.4 10^{-3}); VPC of the isopropyl urethane derivative on the chiral column indicated an enantiomeric purity higher than 99%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.85, 1.03, 1.09, and 1.16 (4 s, 12 H), 1.55 (s, 1 H), 1.70 (dd, J = 13.6 Hz, J = 10.4 Hz, 1 H), 1.88 (dd, J = 13.6 Hz, J = 4.5 Hz, 1 H), 2.20 and 2.40 (2 d, J = 14.3 Hz, 2 H), 3.90 (dd, J = 10.4 Hz, J = 4.5 Hz, 1 H).

Irradiation at 1.8 ppm converted the 3.9 ppm doublet of doublets to a singlet which was significantly shifted (*without splitting*) to lower fields by adding tris[3-((trifluoromethyl)-hydroxymethylene)-*d*-camphorato]europium (III). The same experiment on the (±)-ketol showed clearly, at the same Eu derivative concentration, the presence of *two singlets* ($\Delta\delta$ = 6 Hz). The signal exhibited under these conditions by the *S* ketol was shown to correspond to the upfield singlet, by using an enriched *S* ketol preparation.

A similar reduction of the diketone **3** by *Aspergillus ochraceus* (ATCC 1009) afforded the crystalline *S* ketol **11** in 85% yield after a 10-day incubation. In this case, a small amount (~5%) of one of the diols (retention time, 13.6 min) was detected by VPC on 10% DEGS; it was easily removed by crystallization of the ketol.

(*S*)-4-(Mesyloxy)-2,2,5,5-tetramethylcyclohexan-1-one (12). To a solution of 600 mg of ketol **11** (3.5 mmol) in 10 mL of methylene chloride and 1 mL of triethylamine was added at 0 °C 0.4 mL (0.59 g, 5.2 mmol) of methanesulfonyl chloride. The mixture was then stirred for 30 min at 0 °C. Compound **12** was obtained in 97% yield as crystals: mp 56–57 °C; $[\alpha]^{20}_D$ +60.7° (*c* 2.06, $CHCl_3$); IR (Nujol) 1710 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.95 (s, 3 H), 1.1 (s, 3 H), 1.15 (s, 3 H), 1.2 (s, 3 H), 1.9–2.6 (m, 4 H), 3.0 (s, 3 H), 4.8 (d, J = 6.8 Hz, 1 H).

(1*R*,5*S*)-3,3,6,6-Tetramethylbicyclo[3.1.0]hexan-2-one (13). To a solution of 250 mg (1 mmol) of mesylate **12** in 2 mL of THF was added at −20 °C 1.15 mL of a 1.5 M solution (1.7 mmol) of sodium *tert*-amylate in benzene. The mixture was then stirred for 30 min at 20 °C. Compound **13** was obtained as an oil: $[\alpha]^{20}_D$ +161° (*c* 1.55, MeOH); IR (neat) 1720 cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ 0.9 (s, 3 H), 1.0 (s, 3 H), 1.05 (s, 3 H), 1.15 (s, 3 H), 1.3–2.1 (m, 4 H).

Attempted Baeyer–Villiger Oxidations of Ketone 13. The following experimental conditions were unsuccessful (ketone **13** was recovered in all cases): *m*-Chloroperbenzoic acid (methylene chloride, reflux 12 h), *p*-nitroperbenzoic acid (methylene chloride, reflux 12 h), hydrogen peroxide (30%)/sodium hydroxide (methanol, 40 °C, 10 h), hydrogen peroxide (30%)/sodium monohydrogenophosphate (methanol, 50 °C, 12 h), hydrogen peroxide (30%)/acetic acid[26] (50 °C, 12 h).

(*S*)-4,6-Dihydroxy-3,3,6-trimethylheptanoic Acid γ-Lactone (15). A mixture of 112 mg (0.7 mmol) of ketol **11** and 172 mg of 85% *m*-chloroperbenzoic acid (0.85 mmol) in 2 mL of methylene chloride was stirred at 20 °C during 3 days. Compound **15** was obtained as an oil in 85% yield; $[\alpha]^{20}_D$ −106° (*c* 1.6, MeOH); IR (neat) 3440, 1770 cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ 0.95 (s, 3 H), 1.14 (s, 3 H), 1.25 (s, 6 H), 1.55 (m, 2 H), 2.1 (d, 1 H), 2.38 (d, 1 H), 2.8 (s, 1 H), 4.28 (m, 1 H).

(*S*)-6-Hydroxy-4-(mesyloxy)-3,3,6-trimethylheptanoic Acid ε-Lactone (16). A mixture of 283 mg (1.14 mmol) of mesylate **12** and 330 mg of 85% *m*-chloroperbenzoic acid (1.6 mmol) in 2 mL of methylene chloride was stirred for 4 days at 20 °C. Compound **16** was obtained in 85% yield as crystals: mp 100 °C dec; $[\alpha]^{20}_D$ +24.7° (*c* 1.9, $CHCl_3$); IR (Nujol) 1705 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.1 (s, 3 H), 1.2 (s, 3 H), 1.6 (s, 6 H), 2.4 (m, 2 H), 2.75 (m, 2 H), 3.1 (s, 3 H), 4.8 (dd, J = 6 Hz, J = 6 Hz, 1 H).

(1*R*,6*S*)-4,4,7,7-Tetramethyl-3-oxabicyclo[4.1.0]heptan-2-one, or (+)-Dihydrochrysanthemolactone (17). To a solution of 126 mg (0.48 mmol) of compound **16** in 2 mL of THF was added 0.38 mL (0.57 mmol) of a 1.5 M solution of sodium *tert*-amylate in benzene at 0 °C. The resulting mixture was then stirred for 15 min at 20 °C. Compound **17** was obtained in 95% yield as white crystals: mp 83–84 °C (hexane) (lit.[1n] mp 83 °C); $[\alpha]^{20}_D$ +78° (*c* 1.2, $CHCl_3$) [lit.[1n] $[\alpha]^{20}_D$ +77.6° (*c* 1.8, $CHCl_3$)]; mass spectrum, *m/e* 168 (M^+), 153, 124, 109, 95, 81, 67, 55, 43; IR (Nujol) 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 3 H), 1.22 (s, 3 H), 1.34 (s, 3 H), 1.41 (ddd, J = 5.1 Hz, J = 7.7 Hz, J = 9.7 Hz, 1 H), 1.44 (s, 3 H), 1.55 (d, J = 7.7 Hz, 1 H), 1.65 (dd, J = 5.1 Hz, J = 15.0 Hz, 1 H), 1.92 (dd, J = 9.7 Hz, J = 15.0 Hz, 1 H).

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