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NOVEL SYNTHESIS OF VINYL CYCLOPROPANE CARBOXYLIC ACIDS : APPLICATION TO THE SYNTHESIS OF *(d,l)*- AND *(d)-CIS*-CHRYSANTHEMIC ACID

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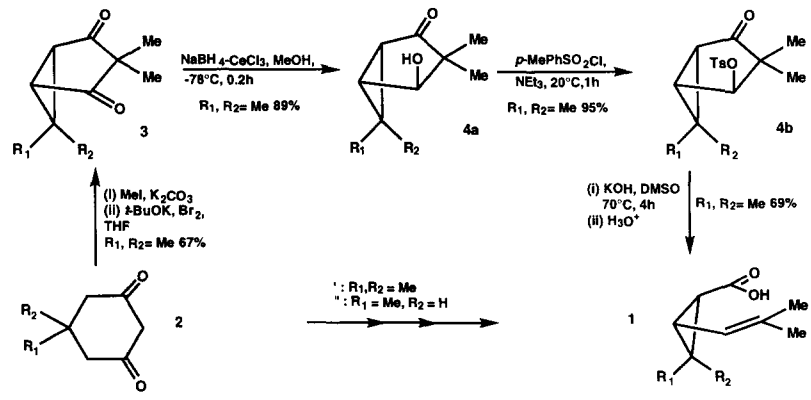
Abstract: Reaction of sulfur ylides with suitably 4-functionalized-5,5-dimethyl-2-cyclopentenones allows an efficient entry to the bicyclo[3.1.0]hexan-2-one skeleton which proved to be a valuable precursor of vinyl cyclopropane carboxylic acids. Application to the synthesis of *(d,l)*- and *(d)-(cis)*-chrysanthemic acid is described.

A few years ago, we disclosed[1a,b] the synthesis of *(d,l)-cis*-chrysanthemic acid **1'** (R_1, R_2 = Me)[2] from dimedone **2'** as the starting material. The main steps of this synthesis involve (i) geminal dialkylation of dimedone, (ii) oxidative cyclisation of dimethyl dimedone, (iii) reduction of the resulting bicyclic dione **3'** and (iv) tosylation of the β-hydroxy ketone intermediate **4'a** followed by Grob fragmentation (Scheme 1).

Scheme 1

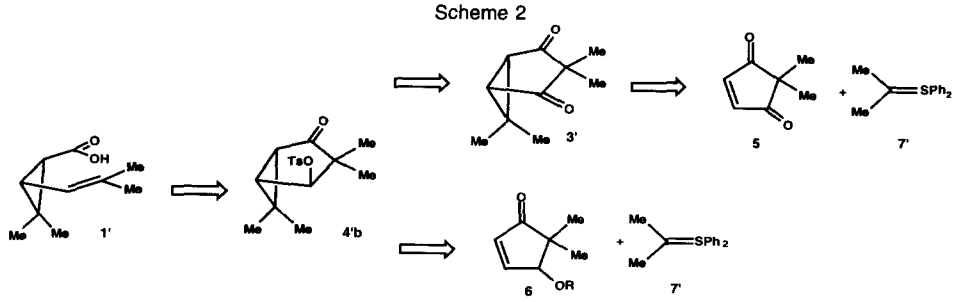


The key step of this approach is without doubt the synthesis of the β-hydroxy ketone **4'a**, the only isomer leading to **1'**. It requires the chemo- and stereoselective reduction of one of the carbonyl groups of **3'** by its most hindered face, successfully achieved by $NaBH_4$-$CeCl_3$.[1a,b]

We now report novel and highly convergent syntheses of *(d,l)-cis*- and *(d)-cis*-chrysanthemic acids from bicyclo[3.1.0]hexane derivatives[1] **3'**, **4'a** and **4'b** involving the cyclopropanation of 2,2-dimethyl-4-cyclopenten-1,3-dione **5**,[3] 4-hydroxy-5,5-dimethyl-cyclopent-2-en-1-one **6a**,[3] and related compounds **6b-e**[3] with isopropylidenediphenyl sulfurane **7'** (enone, 1.2 eq. $Ph_2S{=}CMe_2$ $LiBF_4$, DME, - 78°C, 1h then 20°C, 1h). The latter is prepared *in situ* by metallation of the corresponding sulfonium tetrafluoroborate salt (1.2 eq. Ph_2S-$CHMe_2$ BF_4, 1 eq. LDA, 1 eq. CH_2Cl_2, DME, - 78°C, 0.5 h).[4]

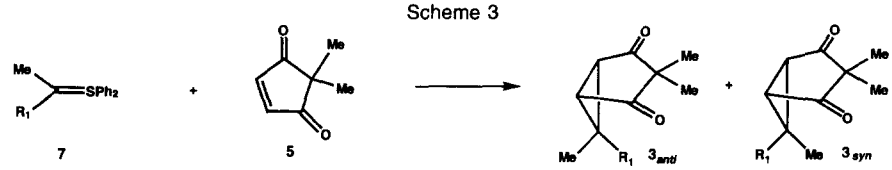
Dedicated to the memory of Professor Wolfgang Opplozer : a good friend and a fine chemist.

Scheme 2



Although it is highly polymerisable, the 4-cyclopentene-1,3-dione **5** efficiently reacts with isopropylidenediphenylsulfurane **7'** and produces the desired bicyclic dione **3'** in reasonably good yield (Scheme 3, entry a).

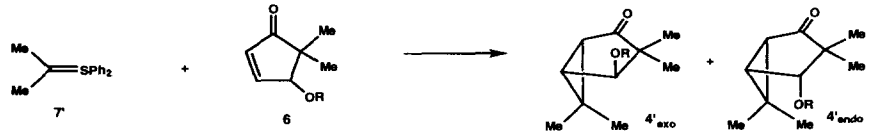
Scheme 3



Entry	R_1	ylide	Enone	Product	Yield	*anti*	*syn*
a	Me	**7'**	**5**	**3'**	74	-	-
b	H	**7"**	**5**	**3"**	80	96	4

The reaction of the same ylide on the 4-hydroxy- **6a**, 4-tosyloxy- **6b**, 4-silyloxy- **6c** or **6d** and 4-acetoxy- **6e** enones is completely chemo- and stereoselective and leads to the bicyclo[3.1.0]hexane derivatives bearing a free hydroxyl group **4'a** or related derivatives bearing an activated (such as **4'b**) or a protected (such as **4'c-e**) hydroxyl group in the *exo*-position (Scheme 4). These are the only stereoisomers which can be transformed to chrysanthemic acid **1'**.[1] Interestingly cyclopropanation of **6a** takes place without competitive retro-aldol reaction neither on the starting enone **6a**, nor on the resulting bicyclic derivative **4'a**. Furthermore, cyclopropanation of **6'b** occurs without any concomitant reaction on the allylic tosylate moiety and allows a very convergent and straightforward approach to *(d,l)-cis*-chrysanthemic acid **1'**.[1a]

Scheme 4



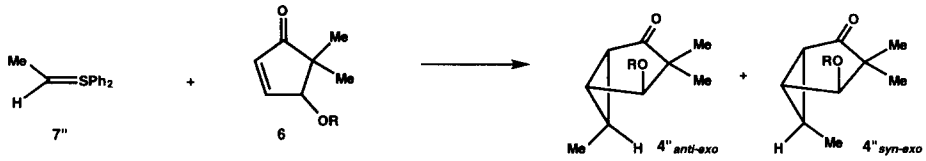
Entry	Ylide	Enone	R	Product	Yield	*exo*	*endo*
a	**7'**	**6a**	H	**4'a**	70	100	0
b	**7'**	**6b**	Ts	**4'b**	79	100	0
c	**7'**	**6c**	TMS	**4'c**	76	100	0
d	**7'**	**6d**	TBDMS	**4'd**	79	100	0
e	**7'**	**6e**	Ac	**4'e**	81	100	0

We have extended this reaction to ethylidenediphenyl sulfurane **7"**.[4a,6a] Although we expected the results to be more complex, the reaction proceeded stereoselectively on the 2,2-dimethyl-4-cyclopenten-1,3-dione **5** leading mainly to the bicyclic derivative bearing the methyl group in *anti*-position **3"** (d.e. 92 %, Scheme 3, entry b).

The reaction is still high yielding but by far less stereoselective when carried out on the hydroxy enone **6a** or on its derivatives **6b-e**.

The *anti-exo* **4"a** stereoisomer is the major product obtained from the hydroxy enone **6a** (Scheme 4, entry a) accompanied by trace amounts of the three other stereoisomers (5% each) whereas equal amounts of the *anti-exo* and the *syn-exo* stereoisomers **4"e** are generated from its acetoxy derivative **6e** (Scheme 5, entry b).

Scheme 5

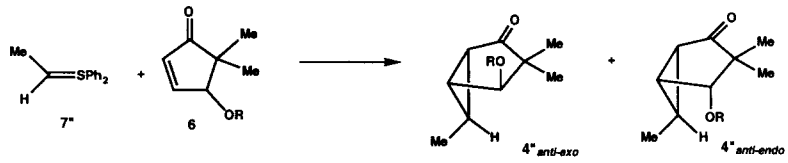


Entry	Ylide	Enone	R	Product	Yield	*anti-exo*	*syn-exo*
a	**7'**	**6a**	H	**4"a**	80 *	85	5
b	**7'**	**6e**	Ac	**4"e**	86	50	50

* The *anti-endo* and *syn-endo* stereoisomers are also formed in 5% each.

Surprisingly the reaction takes another course with the closely related silyloxy derivatives **6c-d** (Scheme 6). Cyclopropanation of trimethylsilyloxy derivative **6c** provides a 1.6/1 mixture of *anti-exo* and *anti-endo* stereoisomers **4"c** resulting from the attack of the ylide from each of the two faces of the enone **6c**. More surprising is the even higher percentage of the *anti-endo* stereoisomer **4"d** arising from the attack of the ylide from the most hindered of the two faces of the enone **6d** bearing the particularly bulky *t*-butyldimethylsilyloxy group at its 4-position.

Scheme 6



Entry	Enone	R	Product	Yield*	*anti-exo*	*anti-endo*
a	**6c**	TMS	**4"c**	85	36	58
b	**6d**	TBDMS	**4"d**	82	30	68
c	**6b**	Ts	**4"b**	82	64	30

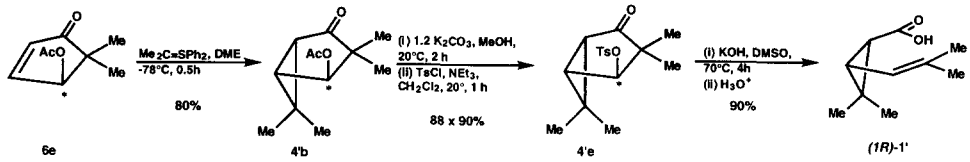
* The *syn-exo* stereoisomers are also formed in 6, 2 and 6% respectively.

We have also found that the 4-tosyloxy enone **6b** possesses a similar reactivity to that of the silyl derivatives, although the *anti-endo* stereoisomer **4"b** is no longer the predominant one.

Most of the compounds reported here are known and their stereochemistry already established.[1a-c] It was easy to compare their spectra to those of authentic samples and therefore to determine their structure unambiguously.

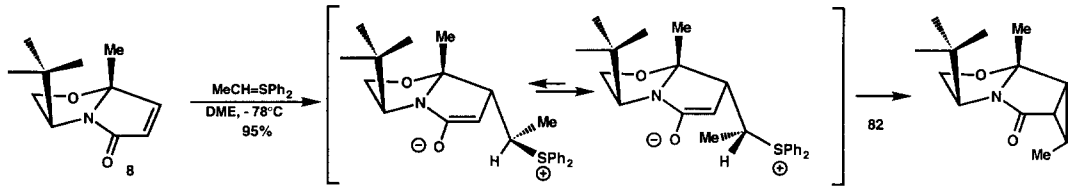
Finally the reaction of isopropylidenediphenyl sulfurane **7'** with the readily available optically active 4-acetoxycyclopentenone **6e**[3] allows the highly enantioselective synthesis of the bicyclo[3.1.0]cyclohexanone **4'e**[5] from which *(1R)-cis*-Chrysanthemic acid has been synthesized (Scheme 7).[1d]

Scheme 7



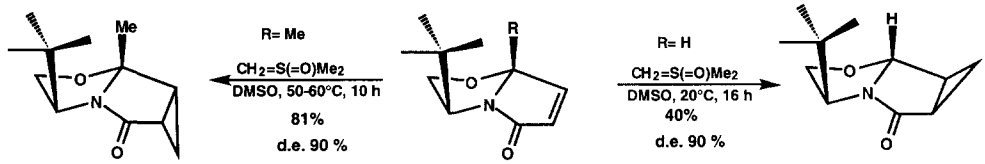
Most of the reactions reported here produce the most stable stereoisomers *via* transition states involving the weakest steric interactions (Schemes 3, 4, 5 entry a). Few others involving ethylidenediphenyl sulfurane **7'** and 4-acetoxy- **6e**, 4-silyloxy- **6c-d** or 4-sulfonyloxy- **6b** enones (Schemes 5 entry b, Scheme 6) lead to results which are not consistent with this interpretation. In such cases, electronic interactions are expected to dominate the above mentioned steric effects and might be responsible for these discrepancies. More work is required to clearly rationalize all these results. For example, the formation of *syn*-cyclopropyl derivatives, related to the reaction we just reported from ethylidenediphenyl sulfurane **7"** and a bicyclic unsaturated lactame **8**, has been explained by Meyers by the addition of the ylide with the lowest steric interaction followed by a rotation in order to attain proper alignment of the leaving sulfonium group in an S_N2 type reaction (Scheme 8).[6a]

Scheme 8



The same author has attempted to explain, but without success,[6b] results related to those we have reported here using the Cieplak[6c-d] stereoelectronic model (Scheme 9).

Scheme 9



REFERENCES AND NOTES

1. (a) Krief, A.; Surleraux, D.; Frauenrath, H. *Tetrahedron Lett.* **1988**, *29*, 6157 (b) Krief, A.; Surleraux, D. *Synlett* **1991**, 273 (c) Krief, A.; Surleraux, D.; Robson, M.J. *Synlett* **1991**, 276 (d) Krief, A.; Surleraux, D.; Ropson, N. *Tetrahedron: Asymmetry* **1993**, *4*, 289.
2. Krief, A. in "Stereocontrolled Organic Synthesis. A 'Chemistry for the 21st Century' Monograph", *International Union of Pure and Applied Chemistry*, Trost, B.M., Ed; Blackwell Scientific Publications **1994**, 337.
3. Kreiser, W.; Wiggermann, A.; Krief, A. ; Swinnen, D. accompanying paper.
4. (a) Corey, E. J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* **1967**, 2325 (b) Corey, E. J.; Jautelat, M. *J. Am. Chem. Soc.* **1967**, *89*, 3912 (c) Sevrin, M.; Hevesi, L.; Krief, A. *Tetrahedron Lett.* **1976**, 3915 (d) Krief, A.; Dumont, W.; Pasau, P.; Lecomte, Ph. *Tetrahedron* **1989**, *45*, 3039 (e) Krief, A.; Lecomte, Ph; Demoute, J.P.; Dumont, W. *Synthesis* **1990**, 275 (f) Romo, D.; Romine, J. L.; Midura, W.; Meyers, A. I. *Tetrahedron* **1990**, *46*, 4951.
5. This work $[a]_D^{20}$ = + 76.8 (c= 1.05, $CHCl_3$) , literature $[a]_D^{20}$ = + 77.6 (c= 1.85, $CHCl_3$) [1d]
6. (a) Romo, D.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 6265 (b) Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509. (c) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540 (d) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875.

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