J. Org. Chem. **1990**, *55*, 501-504

Epoxide Synthesis in Interfacial Solid–Liquid Conditions

E. Borredon,*[,†] F. Clavellinas,[‡] M. Delmas,[†] A. Gaset,[†] and J. V. Sinisterra[‡]

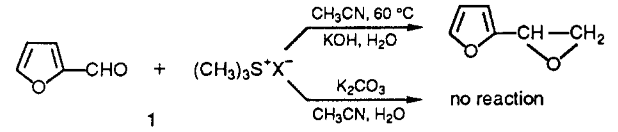
Laboratoire de Chimie des Agroressources, Ecole Nationale Supérieure de Chimie, 118 route de Narbonne, 31077 Toulouse Cêdex, France, and Departamento de Quimica Organica y Farmaceutica Faculta de Farmacia, Universidad Complutense Madrid, Spain

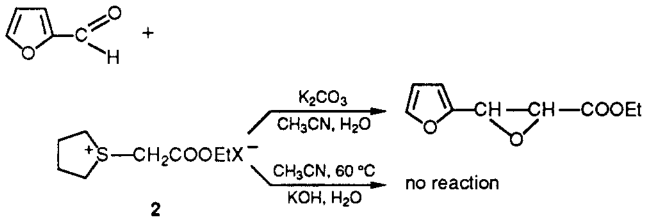
Received June 21, 1988

In this paper an analysis of the factors responsible for discrimination among differing structures of organic reagents by the microcrystalline structure of solids is presented. As a vehicle for this study, the epoxide synthesis using three sulfur ylide precursors (sulfonium and sulfoxonium salts) and four microcrystalline solids was investigated. Neither the surface area nor the number of active sites at the solid surface control the epoxide yield. It appears that the cell lattice of the solid determines the ylide structure, its nucleophilicity, and thus the reaction yield.

The sulfur ylides are a well-known class of compounds that have been used in the synthesis of epoxides since the early work of both Johnson[1] and Corey.[2] Sulfonium and sulfoxonium ylides have been employed in this capacity. The latter can be obtained from the corresponding sulfonium or sulfoxonium salts by using strong bases in anhydrous media,[2,3] and more recently under phase-transfer catalysis (PTC) conditions,[4] or in slightly hydrated solid–liquid media.[5] This methodology gives better yields than the homogeneous process and is a more straightforward procedure.[5]

Nevertheless, the solid seems to play an important role in the process, as we have shown previously[6a] in the reaction of trimethylsulfonium salt, **1**, or ethyl 2-(1-tetrahydrothiophenio)acetate, **2**, with furfural. Moreover, we demonstrated that sulfonium ylide is formed and reacts with the aldehyde at the solid–liquid interface and not in the organic phase.[6b]





To study this effect, a more detailed study was conducted using **1**, **2**, and trimethylsulfoxonium iodide, **3**, as sulfur ylide precursors. Four basic solids with different microcrystalline structures were used: commercial KOH, K_2CO_3, barium hydroxide (C–O), and an activated barium hydroxide catalyst, C-200.

In this paper we offer an analysis of the factors that allow discrimination among differing structures of ylide precursors by a microcrystalline solid, leading to variation in product yields. In addition, an explanation for how the ylide precursor, in turn, can distinguish one structure of basic solid from another, giving reaction in some cases and not in others, is advanced.

Table I. Surface Area and Number of Active Sites of the Basic Catalysts

catalyst	surf. area, $m^2 g^{-1}$	no. of active sites, μequiv g^{-1} reducing sites vs DNB	no. of active sites, μequiv g^{-1} strong basic sites vs vs TBMPHE
C–O	1.4 ± 0.1	55 ± 5	260 ± 30
C-200	1.9 ± 0.1	35 ± 4	6.3 ± 0.2
$K_2CO_3 \cdot 1.5H_2O$	2.1 ± 0.2	95 ± 10	80 ● 8
$KOH \cdot H_2O$	1.6 ± 0.2	110 ± 22[a]	*b*

[a] The solid is slowly dissolved during the titration with 1,3-dinitrobenzene (DNB). [b] The solid is dissolved by the titrating solution of 4-methyl-2,6-di-*tert*-butylphenol (TBMPHE).

Results and Discussion

Structures of the Basic Solids. Four different basic solid catalysts were tested: activated barium hydroxide, C-200,[7,8] and the three commercial basic solids C–O ($Ba(OH)_2 \cdot 8H_2O$),[8] K_2CO_3 ($K_2CO_3 \cdot 1.5H_2O$), and KOH ($KOH \cdot H_2O$), whose empirical formulas (determined by TGA and X-ray analysis) is given in parentheses.[6,8] C-200 is $Ba(OH)_2 \cdot 0.2H_2O$, according to TGA analysis.[8]

The surface areas (Table I) are similar in all cases and therefore cannot be responsible for the observed differences in catalytic activity in the epoxide syntheses. These small surface area values agree with the microcrystalline structures observed in all solids. C-200 is actually a mixture consisting of β-$Ba(OH)_2$ in the bulk solid and $Ba(OH)_2 \cdot H_2O$ at the solid surface,[8] where the average OH^-–H_2O distance is 3.39 Å.

C–O ($Ba(OH)_2 \cdot 8H_2O$) crystallizes in monoclinic systems,[9] and the average OH^-–H_2O distance is 3.09 Å. $K_2CO_3 \cdot 1.5H_2O$ crystallizes in monoclinic systems[10] with an average

---

[†] Ecole Nationale Supêrieure de Chimie.
[‡] Universidad Complutense Madrid.

(1) Johnson, A. W.; Kruby, V. J.; Williams, J. L. *J. Am. Chem. Soc.* **1964**, *86*, 918.
(2) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
(3) Franzen, V.; Driessen, H. E. *Chem. Ber.* **1963**, *96*, 1881.
(4) (a) Hatch, M. J. *J. Org. Chem.* **1969**, *34*, 2133. (b) Merz, A.; Markl, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 845. (c) Rosemberger, M.; Jackson, W.; Sancy, G. *Helv. Chim. Acta.* **1980**, *63*, 1665. (d) Mosset, P.; Gree, R. *Synth. Commun.* **1985**, *15*, 749.
(5) (a) Borredon, E.; Delmas, M.; Gaset, A. French Patent 8208631, 1982; European Patent 8320685, 1983. (b) *Ibid. Biomass* **1983**, *3*, 67. (c) *Ibid Tetrahedron Lett.* **1987**, *28*, 1877. (d) Bouda, H.; Borredon, M. E.; Delmas, M.; Gaset, A. *Synth. Commun.* **1987**, *17*, 503.
(6) (a) Borredon, M. E.; Sinisterra, J. V.; Delmas, M.; Gaset, A. *Tetrahedron* **1987**, *43*, 4141. (b) Borredon, M. E.; Delmas, M.; Gaset, A. *Tetrahedron* **1988**, *47*, 1073.
(7) (a) Garcia-Raso, A.; Garcia-Raso, J. A.; Campaner, B.; Mestre, R.; Sinisterra, J. V. *Synthesis* **1982**, 1037. (b) Sinisterra, J. V.; Mouloungui, Z.; Delmas, M.; Gaset, A. *Synthesis* **1985**, 1097.
(8) Barrios, J.; Rojas, R.; Sinisterra, J. V. *J. Catal.*, in press.
(9) (a) Manohar, H.; Ramasesmam, S. *Curr. Sci.* **1963**, *32*, 248; *Chem. Abstr.* **1963**, *69*, 8212a. (b) *Ibid.-Z. Kristallogr.* **1964**, *119*, 357.

0022-3263/90/1955-0501$02.50/0 © 1990 American Chemical Society

Table II. Epoxide Yields with Barium Hydroxides in Interfacial Solid–Liquid Conditions[d]

entry	4	sulfur salt	solid base	yield, %
1	FuCHO[c]	1	C-O[a]	0
2	C_6H_5CHO	1	C-O[a]	0
3	4-$CH_3OC_6H_4CHO$	1	C-O[a]	0
4	4-$NO_2C_6H_4CHO$	1	C-O[a]	0
5	FuCH=O	2	C-O[a]	30
6	$C_6H_5CH{=}O$	2	C-O[a]	30
7	4-$CH_3OC_6H_4CHO$	2	C-O[a]	0
8	4-$NO_2C_6H_4CHO$	2	C-O[a]	48
9	FuCH=O	3	C-O[b]	18
10	FuCH=O	1	C-200[b]	0
11	FuCH=O	2	C-200[b]	0
12	FuCH=O	3	C-200[b]	38
13	4-$CH_3OC_6H_4CHO$	3	C-200[b]	0
14	4-$CH_3C_6H_4CHO$	3	C-200[b]	5
15	3-$NO_2C_6H_4CHO$	3	C-200[b]	79
16	4-$NO_2C_6H_4CHO$	3	C-200[b]	100

[a] T = 50 °C; molar ratio of C-O/4 = 3. [b] T = 60 °C. [c] Fu = furan-2-yl. [d] 12 mmol of **1**, **2**, or **3**; 12 mmol of **4**; 2 g of solid base; 30 mL of CH_3CN; 5 mmol of H_2O; 60 min.

Table III. Epoxide Yield with Commercial KOH and K_2CO_3 in Interfacial Solid–Liquid Conditions[a]

entry	4	sulfur salt	solid base	yield, %
1	FuCHO	1	$COH{\cdot}H_2O$[b]	80
2	4-$NO_2C_6H_4CHO$	1	$KOH{\cdot}H_2O$[b]	95
3	4-$CH_3OC_6H_4CHO$	1	$KOH{\cdot}H_2O$[b]	90
4	FuCHO	2	$KOH{\cdot}H_2O$[b]	0
5	FuCHO	3	$KOH{\cdot}H_2O$[b]	5
6	C_6H_5CHO	3	$KOH{\cdot}H_2O$[b]	60
7	4-$CH_3OC_6H_4CHO$	3	$KOH{\cdot}H_2O$[b]	90
8	FuCHO	1	$KOH{\cdot}H_2O$[b]	0
9	FuCHO	2	$K_2CO_3{\cdot}1.5H_2O$[c]	79
10	FuCHO	3	$K_2CO_3{\cdot}1.5H_2O$[c]	0
11	4-ClC_6H_4CHO	2	$K_2CO_3{\cdot}1.5H_2O$[c]	64
12	3-$NO_2C_6H_4CHO$	2	$K_2CO_3{\cdot}1.5H_2O$[c]	63
13	4-$NO_2C_6H_4CHO$	2	$K_2CO_3{\cdot}1.5H_2O$[c]	69
14	4-$MeOC_6H_4CHO$	2	$K_2CO_3{\cdot}1.5H_2O$[c]	14
15	4-MeC_6H_4CHO	2	$K_2CO_3{\cdot}1.5H_2O$[c]	11

[a] T = 60 °C; 20 mmol of **1**, **2**, or **3**; 20 mmol of **4**; 50 mmol of H_2O; 30 mL of CH_3CN. [b] T = 52 °C; V = 30 mL of CH_3CN. Molar ratio of KOH/salt = 1. [c] Molar ratio of K_2CO_3/salt = 6.

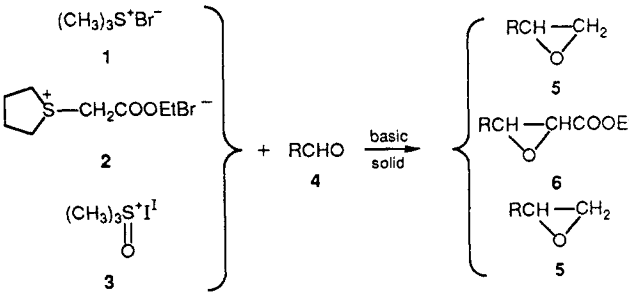
CO_3^{2-}–H_2O distance of 5.1 Å. The commercial KOH was $KOH{\cdot}H_2O$, partially carbonated, with an average OH^-–H_2O distance of 5.8 Å.[6] Thus, we have two different kinds of solids: (i) the barium hydroxides, with a small average OH^-–H_2O distance (3.39 Å in C-200 and 3.09 Å in C–O), and (ii) the commercial KOH and K_2CO_3, with a large anion (OH^- or CO_3^{2-})–H_2O distance (5.1 Å in $K_2CO_3{\cdot}1.5H_2O$ and 5.8 Å in $KOH{\cdot}H_2O$).

All the solids have exclusively reducing sites with respect to 1,3-dinitrobenzene (DNB) and strongly basic sites ($pK_a > 11.7$) with respect to 4-methyl-2,6-di-*tert*-butylphenol (TBMPHE, see Table I). There are neither oxidizing sites titratable by phenothiazine nor acid sites titratable by pyridine or cyclohexylamine. The active sites were titrated by a method described previously.[11]

The number of reducing sites decreases in the sequence $KOH{\cdot}H_2O > K_2CO_3{\cdot}1.5H_2O >$ C–O > C-200, and the strong basic sites decrease in the order C–O > $K_2CO_3{\cdot}1.5H_2O >$ C-200.

The $KOH{\cdot}H_2O$ reacts with the cyclohexane solution of TBMPHE to dissolve the solid. Therefore, the number of strong basic sites in this solid cannot be determined.

Epoxide Syntheses. To analyze the influence of the nature of the ylide precursor on the epoxide yield, three different parent compounds were used: two sulfonium salts with different structures and pK_a's of the α-hydrogen atoms, **1** and **2**, and the sulfoxonium salt **3**.



The results are shown in Tables II and III.

The optimization of the synthetic procedure has been published in previous papers.[5]

From the data of Table II we can deduce that both barium hydroxides (C–O and C-200) are not active with respect to **1** (entries 1 and 10). Nevertheless, C–O does react with the more acidic sulfonium salt **2** (pK_a = 7.68),[12] when a very electrophilic aldehyde is used (entries 5, 6, and 8). Under the same conditions, C-200 does not give reaction. The microcrystalline structures of C–O and C-200 remain intact following reaction, according to X-ray powder diagrams.

From the data of Table III, we can deduce that while $K_2CO_3{\cdot}1.5H_2O$ is catalytically active with respect to **2** (entries 9, 11–15), $KOH{\cdot}H_2O$ is active with respect to **1** (entries 1–3) and **3** (entries 5–7). This difference in behaviors cannot be explained by either the number of basic sites or the surface area values (Table I). All of the solids contain strongly basic sites ($pK_a > 11.7$), which could catalyze the process. The surface areas are small (due to the microcrystalline structures of the solids) and of a similar value. Thus, these factors cannot account for the different reactivities observed. Instead, the discrepancy must arise from some intrinsic properties of the solids, such as the cell lattice.

The very weak acid $(CH_3)_2{}^+SCH_2$–H (pK_a = 18.9)[13] reacts only with the strong base $KOH{\cdot}H_2O$. Nevertheless, the pK_a of the sulfur salt is not a reliable indicator of the reaction pathway, as **3** reacts in the presence of $KOH{\cdot}H_2O$ as well as with C-200. However, the behavior is completely different. With $KOH{\cdot}H_2O$, the electron-donating character of the substituent of the aldehyde favors the process (Table III, entries 3 and 7), while the same substituent discourages the process with the activated barium hydroxide (Table II, entries 13 and 14).

On the other hand, the strong acid **2** reacts in the presence of weak base ($K_2CO_3{\cdot}1.5H_2O$) but not with the strong base $KOH{\cdot}H_2O$. The more hydrated barium hydroxide, C–O, reacts with electrophylic aldehydes (Table II, entries 5, 6, and 7), but the less hydrated barium hydroxide, C-200, does not catalyze the process.

Thus, geometric factors arising from the microcrystalline structure of the solid are clearly the determining factors in the degree of catalytic activity that can be obtained.

Adsorbed Ylides. To explain the different catalytic behaviors observed in the synthesis of epoxides (Tables II and III), the structures of the adsorbed ylides were analyzed by of FTIR; the PECDS program was used in executing the additions and subtractions of spectra. The

---

(10) Mouloungui, Z. Ph.D. Thesis, INP, Toulouse, 1987.

(11) (a) Sinisterra, J. V.; Garcia-Blanco, F.; Iglesias, M.; Marinas, J. M. *React. Kinet. Catal. Lett.* **1984**, *25*, 277. (b) *Ibid.* **1985**, *27*, 263.

(12) Johnson, A. W.; Amel, R. T. *J. Org. Chem.* **1969**, *34*, 1240.

(13) Crosby, J.; Stirling, C. J. M. *J. Chem. Soc., B* **1970**, 671.

(14) Habashy, G. M.; Kolta, G. A. *J. Inorg. Nucl. Chem.* **1972**, *34*, 57.

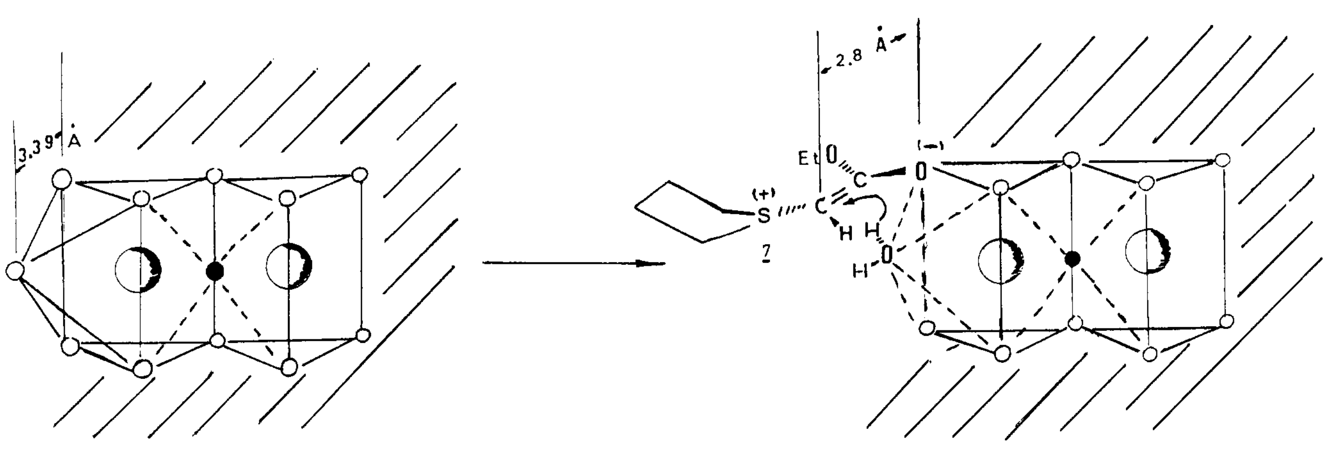


Figure 1. Cell lattice of $Ba(OH)_2{\cdot}H_2O$ and postulated structure of adsorbed ylide 7.

Table IV. Main IR Absorptions (cm^{-1}) of 2 and Its Ylide Adsorbed on C-200 and $K_2CO_3{\cdot}1.5H_2O$

		ylide adsorbed on	
	2	C-200	$K_2CO_3{\cdot}1.5H_2O$
ν(C=O)	1740		
ν(C=O)		1640	1712
ν(C=O)		1612	*a*

[a] Not observable because of the presence of the large absorptions due to bending and rocking of H_2O (1650 and 1560 cm^{-1})[14] in $K_2CO_3{\cdot}1.5H_2O$.

main IR bands of the adsorbed species on C-200 and $K_2CO_3{\cdot}1.5H_2O$ from **2** are shown in Table IV.

We observe the presence of two bands, at 1640 and 1612 cm^{-1} in the difference spectrum, corresponding to the ylide from **2** on C-200. There is no conventional C=O band, (1740 cm^{-1}) but an absorption due to a significantly elongated carbonyl (1640 cm^{-1}) is observed. Absorptions between 1680 and 1650 cm^{-1} have been described as arising from phosphate ylides adsorbed on C-200.[15] Therefore, the adsorbed species on C-200 could be quantitatively described by **7** (Figure 1), according to the microcrystalline structure.[8]

No strongly carbanionic character is present in the CH of **7**, and no reaction with aldehydes would be possible, according to the results (Table II, entry 11).

If we assume the presence of this monoadsorbed species, the water molecule from the $Ba(OH)_2{\cdot}H_2O$ cell lattice would not be removed during the adsorption of **2** that leads to **7**. This molecule is an acid with respect to **7**; thus **7** would be destroyed by the water.

When the adsorption of **2** on $K_2CO_3{\cdot}1.5H_2O$ is carried out, and the IR of the adsorbed species recorded, the carbonyl of the ester group appears at 1712 cm^{-1}. Thus, in this case, the ylide has greater carbanionic character is the CH carbon than in the case of the adsorbed species on C-200. Therefore, $K_2CO_3{\cdot}1.5H_2O$ should be more active than C-200 as an epoxidation catalyst, using **2** as the ylide precursor as is confirmed by the data in Tables II (entry 11) and III (entry 9).

Thus, the cell lattice structures of C-200 and $K_2CO_3{\cdot}1.5H_2O$ are clearly implicated as the primary factors that determine the level of catalytic activity observed, with respect to a single ylide precursor. Similar conclusions regarding the Wittig reaction have been reported, based on ^{31}P NMR evidence.[17]

Experimental Section

Catalysts. The C-200 catalyst was obtained by a method described previously.[7a,18] $K_2CO_3{\cdot}1.5H_2O$ and $KOH{\cdot}H_2O$ were purchased from Fluka Chemicals. C-O ($Ba(OH)_2{\cdot}8H_2O$) was obtained from Probus S.A. The surface areas of the basic catalysts were determined by a Sorptimatic Carlo-Erba. The nature and number of catalytic active sites were determined according to the method described previously.[11] 4-Methyl-2,6-di-*tert*-butylphenol (TBMPHE, $pK_a = 11.7$) was used to titrate the basic sites. 1,3-Dinitrobenzene (DNB, EA = 2.21 eV) was used as the titrating agent for reducing sites. X-ray diffraction diagrams of the catalysts were recorded on a Philips P.W. 1130 diffractometer using monochromatic Co Kα radiation.

Synthetic Procedure. 1-[(Ethoxycarbonyl)methyl]tetrahydrothiophenium Bromide (2). The synthesis of **2** was carried out by first dissolving 250 mL (2.97 mol) of tetrahydrothiophene (Ega-Chemie) in 100 mL of dry acetone. Then, 318 mL of ethyl bromoacetate (2.97 mol, Ega-Chemie) was added slowly. The mixture was cooled in an ice–water bath during the addition. Then, the mixture was heated at the reflux temperature of acetone for 24 h. The sulfonium salt was filtered and washed with dry acetone.

Epoxide Synthesis. Using Trimethylsulfonium Bromide (1) and $KOH{\cdot}H_2O$. **1** (20 mmol), powdered potassium hydroxide (20 mmol), 20 mL of the organic solvent, and the required amount of water were successively introduced into a 100-mL reaction vessel equipped with a reflux condenser and a mechanical stirrer. The reaction mixture was stirred at 52 °C for 15 min. Then the aldehyde (20 mmol) was dissolved in 20 mL of solvent and added slowly to the reaction medium. When the reaction was complete (60 min), the mixture was filtered. The solid phase (KBr and excess $KOH{\cdot}H_2O$) was then washed with ether. The epoxide was recovered after evaporation of the solvent: its purity was above 95%. It could be further purified either by silica gel column chromatography using an ether–hexane mixture as eluent or by distillation.[5a]

Using 2 and $K_2CO_3{\cdot}1.5H_2O$. Base (120 mmol), 20 mL of acetonitrile, 50 mmol of water, and 20 mmol of sulfonium salt were mixed and stirred for 15 min at 60 °C. Then, the aldehyde (20 mmol) was dissolved in 20 mL of solvent and added slowly to the reaction mixture. At the completion of reaction (60 min), the mixture was filtered. The epoxide was purified as above.

Using Trimethylsulfoxonium Iodide (3) and C-200. **3** (2.65 g, 12 mmol, Ega-Chemie) and 2.0 g of C-200 catalyst were mixed in 20 mL of acetonitrile (Ferosa S.A.) with 5 mmol of water. The reaction mixture was stirred at 60 °C for 15 min. Then the aldehyde (12 mmol) dissolved in 10 mL of acetonitrile was added slowly. During the aldehyde addition, the mixture turned orange. At the completion of the reaction (60 min), the mixture was filtered. The epoxide was purified as above.

---

(15) (a) Sinisterra, J. V.; Alcantara, A. R.; Marinas, J. M. *J. Colloid Surf. Sci.* **1987**, *115*(2), 520. (b) Sinisterra, J. v.; Fuentes, A.; Marinas, J. M. *J. Org. Chem.* **1987**, *52*, 3875.

(16) Sinisterra, J. V.; Marinas, J. M.; Riquelme, F.; Arias, M. S. *Tetrahedron* **1988**, *44*, 1431.

(17) Climent, S.; Marinas, J. M.; Mouloungui, Z.; Le Bigot, Y.; Delmas, D.; Gaset, A.; Sinisterra, J. V. *J. Org. Chem.*, in press.

Analysis of the Products. The yields obtained with 1 and 2 were determined by gas chromatography using an Intersmat IGC 120 DFL chromatograph equipped with an in-flame ionization detector and an OV 17 (10%) column, operating isothermically at 160 °C.

In the case of 3, the products were analyzed by a Perkin-Elmer Series 2/HPLC, using a 5-μm C_{18} column and $NaOH/H_2O$ 80/20 (v/v) as eluent; the flux was 1.2 mL/min.

IR Spectra of Adsorbed Species. General Procedure. The adsorption experiments were carried out under conditions analogous to those described in the experimental procedure. The adsorption time was reduced to one-third the reaction time to avoid decomposition of the adsorbed carbanion.

The solid was filtered and washed with clean solvent to eliminate the physisorption of molecules of reagent and then dried under vacuum. The IR spectra of these solids were recorded on a Perkin-Elmer 599 B IR spectrometer using Perkin-Elmer 3600 data station for the accumulation of spectra (PECDS program).

Registry No. 1, 3084-53-5; 2, 25709-55-1; 3, 1774-47-6; 4 (R = Fu), 98-01-1; 4 (R = C_6H_5), 100-52-7; 4 (R = 2-$NO_2C_6H_4$), 555-16-8; 4 (R = 4-$CH_3C_6H_4$), 104-87-0; 4 (R = 3-$NO_2C_6H_4$), 99-61-6; 4 (R = 4-$CH_3OC_6H_4$), 123-11-5; 4 (R = 4-ClC_6H_4), 104-88-1; 5 (R = 4-$CH_3C_6H_4$), 13107-39-6; 5 (R = 3-$NO_2C_6H_4$), 20697-05-6; 5 (R = 4-$CH_3OC_6H_4$), 6388-72-3; 5 (R = Fu), 2745-17-7; 5 (R = C_6H_5), 96-09-3; 5 (R = 4-$NO_2C_6H_4$), 6388-74-5; 6 (R = Fu), 4561-70-0; 6 (R = C_6H_5), 121-39-1; 6 (R = 4-$NO_2C_6H_4$), 109844-94-2; 6 (R = 4-ClC_6H_4), 75755-52-1; 6 (4-MeC_6H_4), 52788-71-3; 6 (3-$NO_2C_6H_4$), 109318-46-9; KOH, 1310-58-3; K_2CO_3, 584-08-7; $Ba(OH)_2$, 17194-00-2.

An Enantioselective Synthesis of (+)-Picrasin B, (+)-Δ^2-Picrasin B, and (+)-Quassin from the *R*-(−) Enantiomer of the Wieland–Miescher Ketone

Moonsun Kim, Kenji Kawada, Raymond S. Gross, and David S. Watt*

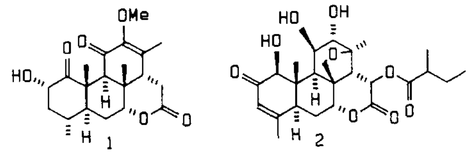
Department of Chemistry, Division of Medicinal Chemistry, Lucille Parker Markey Cancer Center, University of Kentucky, Lexington, Kentucky 40506

Received June 20, 1989

An enantioselective total synthesis of (+)-picrasin B (1), (+)-Δ^2-picrasin B (11), and (+)-quassin (12) from the *R*-(−) enantiomer of the Wieland–Miescher ketone (3) employed an A-AB-ABC-ABCD sequence to assemble the tetracyclic skeleton. The crucial steps in this sequence relied upon a Diels–Alder reaction of a bicyclic AB dienophile 15 with 1-methoxy-2-methyl-3-((trimethylsilyl)oxy)-1,3-butadiene to obtain a tricyclic diol 16, an α'-oxidation of a tricyclic enone intermediate 20 using manganese(III) acetate in order to introduce the C-11 substituent needed to invert the C-9β stereochemistry, and a free-radical cyclization of an α-bromo acetal 23 in order to introduce a protected δ-lactol as a progenitor of the quassinoid D ring.

Recent interest in the quassinoids[1] culminated in ingenious total syntheses[2] of four tetracyclic members of the C_{20} picrasane family in racemic form by groups led by Grieco[3-5] and by Takahashi.[6] Additional interest in enantioselective routes to the quassinoids began with early investigations by Dias[7] and by Graf[8] who selected various steroids and progressed to other imaginative routes devised by Ziegler[9] who employed (+)-carvone as a homochiral source, by Schlessinger[10] who recognized a solution to the stereochemical problems of the C ring of certain quassinoids in α-D-glucose, and by Fukumoto and Kametani[11] who also reported an approach that paralleled the Schlessinger approach.[10] These enantioselective routes, although attractive vehicles for testing the development of new strategies and new synthetic procedures, have not, as yet, reached fruition in terms of a completed total synthesis.

Scheme I



In developing an enantioselective synthesis[12] of tetracyclic quassinoids such as picrasin B[13] (1) and pentacyclic

---

[1] Polonsky, J. *Forts. Chem. Org. Naturst.* **1973**, *30*, 101; **1985**, *47*, 221.

[2] For a review of synthetic work in this area, see: Kawada, K.; Kim, M.; Watt, D. S. *Org. Prep. Proc. Int.* **1989**, *21*, 521.

[3] For a synthesis of (±)-quassin, see: (a) Grieco, P. A.; Ferriño, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7587. (b) Vidari, G.; Ferriño, S.; Grieco, P. A. *Ibid.* **1984**, *106*, 3539.

[4] For a synthesis of (±)-castelanolide, see: (a) Grieco, P. A.; Lis, R.; Ferriño, S.; Jaw, J. Y. *J. Org. Chem.* **1982**, *47*, 601. (b) Grieco, P. A.; Lis, R.; Ferriño, S.; Jaw, J. Y. *Ibid.* **1984**, *49*, 2342.

[5] For a synthesis of (±)-klaineanone, see: Grieco, P. A.; Parker, D. T.; Nargund, R. P. *J. Am. Chem. Soc.* **1988**, *110*, 5568.

[6] (a) Miyaji, K.; Nakamura, T.; Hirota, H.; Igarashi, M.; Takahashi, T. *Tetrahedron Lett.* **1984**, *25*, 5299. (b) Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Takahashi, T. *Ibid.* **1987**, *28*, 435.

[7] (a) Dias, J. R.; Ramachandra, R. *Tetrahedron Lett.* **1976**, 3685. (b) Dias, J. R.; Ramachandra, R. *J. Org. Chem.* **1977**, *42*, 3584. (c) Dias, J. R.; Ramachandra, R. *Ibid.* **1977**, *42*, 1613. (d) Dias, J. R.; Nassim, B. *Steroids* **1980**, *35*, 405. (e) Nassim, B.; Schlemper, E. O.; Dias, J. R. *Ibid.* **1982**, *39*, 531.

[8] (a) Koch, H. J.; Pfenninger, H.; Graf, W. *Helv. Chim. Acta* **1975**, *58*, 1727. (b) Pfenninger, J.; Graf, W. *Ibid.* **1980**, *63*, 1562.

[9] (a) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730; (b) Ziegler, F. E.; Hwang, K.-J.; Kadow, J. F.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Org. Chem.* **1986**, *51*, 4573.

[10] Schlessinger, R. H.; Wong, J.-W.; Poss, M. A.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 3951.

[11] (a) Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1986**, *27*, 1339. (b) Shishido, K.; Takahashi, K.; Fukumoto, K.; Kametani, T.; Honda, T. *J. Org. Chem.* **1987**, *52*, 5704. (c) Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Heterocycles* **1988**, *27*, 495.

[12] For a preliminary account of this work, see: Kawada, K.; Kim, M.; Watt, D. S. *Tetrahedron Lett.*, in press.

[13] This quassinoid has also been called "norquassin" and "nigakilactone I" and "similikalactone B".[11c] (a) Viala, B.; Polonsky, J. *C. R. Acad. Sci., Ser. C* **1970**, *271*, 410. (b) Hikino, H.; Ohta, T.; Takemoto, T. *Chem. Pharm. Bull. (Tokyo)* **1970**, *18*, 219. (c) Tresca, J.-P.; Alais, L.; Polonsky, J. *C. R. Acad. Sci., Ser. C.* **1971**, *273*, 601. (d) Hikino, H.; Ohta, T.; Takemoto, T. *Phytochemistry* **1975**, *14*, 2473. (e) Polonsky, J.; Tri, M. V.; Varon, Z.; Prange, T.; Pascard, C.; Sevenet, T.; Pusset, J. *Tetrahedron* **1980**, *36*, 2983. (f) Park, M. H.; Maeda, M.; Komura, H.; Nakanishi, K.; Nomoto, K. *Chem. Pharm. Bull. (Tokyo)* **1987**, *35*, 3082.

0022-3263/90/1955-0504$02.50/0