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Radical Decarboxylative Alkylation of Tartaric Acid

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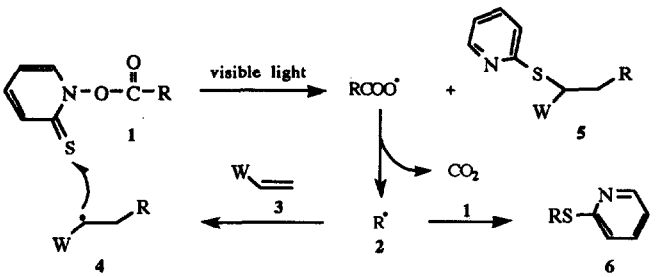
Abstract: *New derivatives of L-(+)-tartaric acid have been synthesized from the monomethyl-2,3-O-isopropylidene (R,R)-(+)-tartrate by visible light photolysis of its N-hydroxy-2-thiopyridone ester derivative in presence of activated alkenes. The carbon radical generated at the dioxolane ring adds stereoselectively to olefins to give the addition products with retention of configuration.*

Tartaric acid, one of the cheapest enantiomerically pure compounds, has been extensively used as a chiral building block for natural products syntheses[1] as well as a ligand for asymetric induction[2]. Both enantiomeric forms {(R,R) and (S,S)} are naturally abundant and the presence of a C_2 axis makes it a valuable starting material. Most transformations have relied heavily on ionic reactions. We have reported some time ago our preliminary results concerning the radical decarboxylative alkylation of tartaric acid[3]. We wish to report here in full the results of our study dealing with the stereoselectivity of the process as well as the facile preparation of highly functionalized derivatives of tartaric acid.

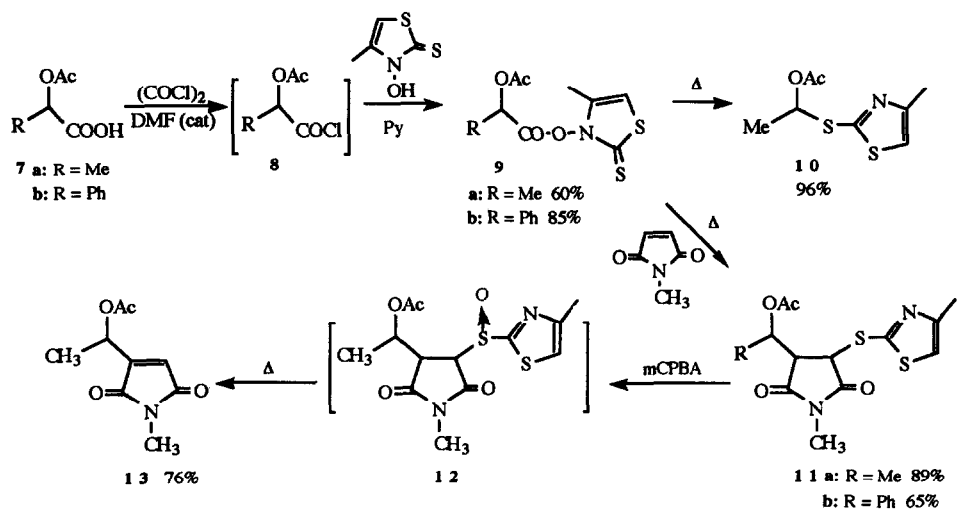
The acyl derivatives of *N*-hydroxy-2-thiopyridone **1** are an excellent source of carbon radicals when photolyzed by visible light[4]. Since its invention this process has also been developed and applied to the generation of nitrogen[5] and oxygen-centered radicals[6]. We have also recently demonstrated that acyl derivatives of type **1** are a substitute for tin hydride[7] and can also be used for the generation of carbon radicals from organo-telluride derivatives[8]. Also other types of thiohydroxamic acids have been synthesized which also undergo radical decarboxylation upon thermolysis and/or UV or visible light photolysis[9].

Among the different ways[10] of trapping carbon radicals, the most useful application concerns C-C bond formation (Scheme 1). In this sequence the carbon radical **2**, generated by visible light photolysis of **1**, is trapped by an electron deficient olefin **3** to give a new radical intermediate **4**. This radical then carries the chain by further reacting with the thiocarbonyl group of **1** to produce the addition product **5** and thus generate a new carbon radical **2**. If the olefin is not radicophilic enough, the intermediate radical **2** can add directly to the thiocarbonyl of **1** to form the sulfide **6** the *so called* "the rearrangement product".



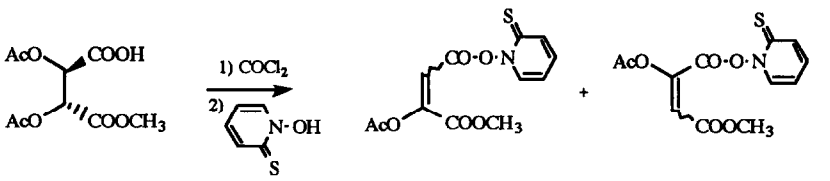
Scheme 1

Our work on tartaric acid was based on earlier results obtained for the radical decarboxylative alkylation of the *O*-acetyl derivatives of L-(+)-lactic **7a** and mandelic **7b** acids (Scheme 2). Our interest was to study the reactivity of α-alkoxy radicals. We found that on refluxing in toluene the 2,3-dihydrothiazole-2-thione ester derivative **9a** leads to the formation of the rearranged product **10** with complete racemisation. This result was not surprising due to the planar geometry of the carbon radical intermediate. When the reaction is carried out in presence of *N*-methylmaleimide the addition products **11a-b** were obtained in modest to good yields. The elimination of the thiazole group by oxidation of the sulfide **11** and thermal elimination of the sulfoxide **12** gave a single product **13**.



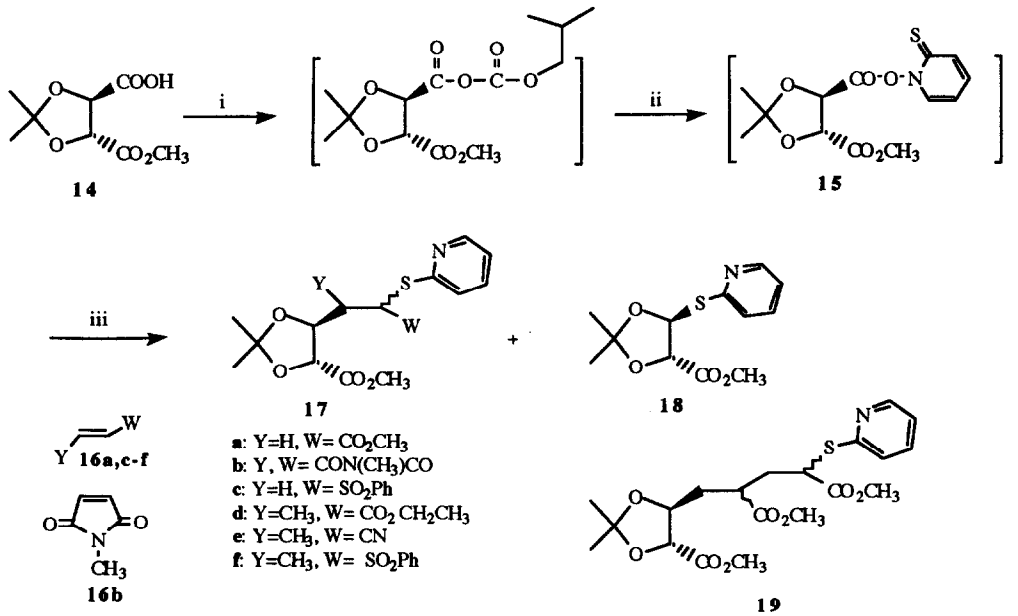
Scheme 2

These results proved that we were able to generate α-alkoxy radicals using the thiohydroxamic acid method. However tartaric acid is a more complicated system that contains two β-hydroxyl moieties known to easily undergo β-elimination to give α,β-unsaturated carbonyl compounds. Indeed our first experiment on an open chain derivative of tartaric acid was unsuccessful. The esterification of the diacetyl monomethylester derivative through the acyl chloride gave a complex mixture of β-elimination products.



To overcome this problem we decided to use a cyclic derivative such as the known isopropylidene monomethyl ester **14** (scheme 3). Also in this case our goal was to be able to keep the stereochemical imprint of the molecule during the process. It was earlier demonstrated that β-substituted cyclopentyl radicals add stereoselectively to alkenes to give predominantly anti addition[11]. We thought the presence of the methyl ester group in our case would ensure an identical stereoselective addition.

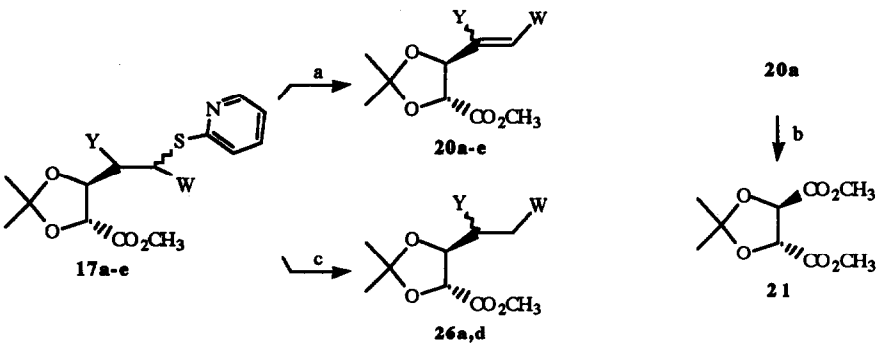
The preparation of the thiohydroxamic ester **15** was finally achieved through the mixed anhydride method[12] at low temperature in THF (Scheme 3). It was not possible to isolate this compound although its formation was confirmed by the characteristic yellow color of the solution.



i: isobutyl chloroformate, *N*-methylmorpholine, THF, - 20°C, 15 min; ii: *N*-hydroxy-2-thiopyridone sodium salt, THF, -20°C, 90 min.; iii: **16**, hv, -20°C, 30 min.

Scheme 3

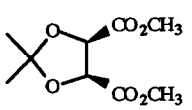
The *in situ* irradiation of **15** was first carried out in absence of olefin and gave the rearranged product **18** as the only isomer detectable by n.m.r. spectroscopy. The coupling constant of the ring hydrogen (J = 5 Hz) did not allow us to determine the cis or trans relationship though steric considerations were in favor of the trans isomer. When the photolysis was effected in presence of methyl acrylate **16a** (5 eq) we observed the formation of the addition product **17a** in 70% yield as a mixture of isomers with respect to the newly created terminal asymmetric center. From the reaction mixture we also isolated a small amount of the rearranged product **18** (2%) and the double addition product **19** (7%). Again the addition of the carbon radical generated during the photolysis of **15** on the methyl acrylate was shown to be stereoselective. In order to determine without doubt the strereochemical assignment of **17a** we decided to convert this compound back into the (R,R) dimethyl isopropylidene tartrate **21** (Scheme 4).



a: i) mCPBA, CH_2Cl_2, 0°C; ii) toluene, reflux, 30 min.; b: i) RuO_2 (cat), $NaIO_4$, $(CH_3)_2CO$, H_2O, r.t., 30 min; ii) CH_2N_2, CH_3CN, r.t., 30 min; c) Ni Raney, EtOH, reflux, 1 hr.

Scheme 4

Peracetic oxydation of the sulfide **17a** (Y=H, W= CO_2Me) to the sulfoxide followed by thermolysis in boiling toluene cleanly afforded the trans olefin **20a** (Y=H, W= CO_2Me) in 75% yield. Cleavage of the double bond with ruthenium dioxide-sodium periodate in acetone-water and methylation of the carboxylic acid intermediate with diazomethane yielded the dimethyl tartrate derivative **21** identical to an authentic sample. The retention of configuration in this radical reaction was thus confirmed. Also HPLC analyses were conducted to further elucidate the stereochemistry of the radical decarboxylative alkylation of **14** in presence of methyl acrylate and to measure the purity of the product formed. The details of this HPLC work has been fully published elsewhere[13]. The results obtained after sequential conversion of **17a** to **21** show the presence of approximately 4% of (R,S)-dimethylisopropylidene tartrate **22** in the crude degradation product.



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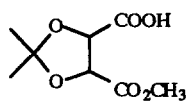

23

An identical study was effected on the racemic (R,S)-monomethyl isopropylidene tartrate **23** derived from the meso tartaric acid. In this case radical decarboxylative alkylation of **23** followed by degradation of the addition product shows the presence of 96% of the racemic mixture (R,R)-(+) and (S,S)-(-)

dimethylisopropylidene tartrate and 4 % of the (R,S) derivative. In this case the radical decarboxylative alkylation gave essentially the addition product with inversion of configuration. These results demonstrate clearly that the process is highly stereoselective (ca. 25:1). It could certainly be improved by replacing the methylester by a bulkier one, by making a more bulky ketal or by lowering the temperature of the reaction.

We have investigated other alkenes **16b-f** in this system which gave adducts **17b-f** (Scheme 3). The results are summarized in Table 1.

Table 1: Radical Decarboxylative Addition of **14** to Olefins **16 a-f.**

Entry	olefin **16**	equivalents	**17** (yield %)	**18** yield (%)
1	**16a** Y= H, W = CO_2CH_3	5	**17a** (70)	2
2	**16b** Y, W = $CON(CH_3)CO$	1.1	**17b** (93)	-
3	**16c** Y= H, W = SO_2Ph	1.5	**17c** (70)	-
4	**16d** Y= CH_3, W = $CO_2C_2H_5$	40	**17d** (55)	6
5	**16e** Y= CH_3, W = CN	40	**17e** (25)	8
6	**16f** Y= CH_3, W = SO_2Ph	10	**17f** (13)	48

Good yields were obtained when the Barton ester **15** was photolysed in presence of *N*-methylmaleimide **16b** or phenyl vinyl sulfone **16c**. The reaction required fewer equivalents of olefin than in the case of methyl acrylate. The additions to **16d** and **16e** gave better yields than we had expected[14]. Both olefins are not easily polymerisable and thus can be used in large excess. This is not the case with methyl acrylate that always gives a small percentage of the two-fold adduct **19** (scheme 3). The methyl phenyl vinyl sulfone **16f** was found to be the least reactive (Table 1, entry 6). During preliminary studies on a model compound **24**[4] we have found that the addition of the adamantyl radical to **16e** and **16g** gave comparable yields of the adducts **25a** and **25c** (Table 2).

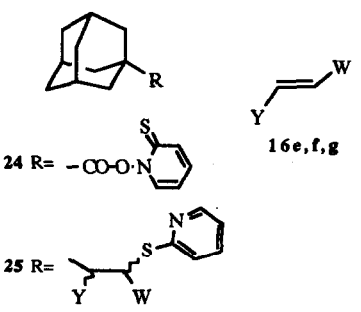

Table 2: Radical Decarboxylative Addition of **24** to Olefins **16 e-g.**

Entry	olefin **16**	equivalents	**25** (yield %)
1	**16e** Y= Me, W = CN	20	**25a** (48)
2	**16f** Y= Me, W = SO_2Ph	10	**25b** (14)
3	**16g** Y= Me, W = CO_2CH_3	30	**25c** (51)

Extensive work has been done in our laboratory on further functionalization of the terminal carbon atom of the newly introduced side chain[15]. A number of useful transformations has been accomplished leading to the formation for example of terminal carboxylic acid, aldehyde, ketone or ketoacid. Also the simple oxidation to sulfoxide and thermal elimination affords olefins. Application of this reaction to the adduct **17** permitted us to obtain the olefins **20a-e**. Similary reduction of **17** with Raney Nickel gave compounds of type **26** (Scheme 4). The results are shown in Table 3.

Table 3: Oxidation-Elimination and Reductive Elimination of the Thiopyridyl Group

Entry	olefin 17	20 (yield %)	26 (yield %)
1	**17a** Y= H, W = CO_2CH_3	**20a** (75)	**26a** (84)
2	**17b** Y, W = $CON(CH_3)CO$	**20b** (52)	-
3	**17c** Y= H, W = SO_2Ph	**20c** (64)	-
4	**17d** Y= CH_3, W = $CO_2C_2H_5$	**20d** (70)	**26d** (80)
5	**17e** Y= CH_3, W = CN	**20e** (50)	-

In conclusion, we have demonstrated that the application of the radical decarboxylative alkylation to the tartrate acetal **14** permitted a simple preparation of some tartaric acid derivatives of synthetic potential. We had planned our work with the tartaric acid derivative in 1985 with the assumption that the radical therefrom would give, on the basis of relative steric hindrance, preferentially the trans compound. We were surprised at the 25:1 selectivity we observed. Later the dimethyl ketal group was used again in nucleoside chemistry with equally satisfactory results[16]. There has been remarkable progress recently in acyclic stereochemical control in free radical reactions using chiral auxiliaries[17]. In fact the problem of stereoselectivity in all kinds of radical chemistry seems to be largely resolved.

Experimental

Melting points were taken on a Reicher apparatus and are not corrected. IR spectra were recorded on a Perkin Elmer 297 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Brüker WP200 SY (200 MHz) or on a HS80 (80 MHz) in $CDCl_3$. Chemical Shifts are in p.p.m. downfield from tetramethylsilane used as an internal standard (δ values). Mass spectra were run on AEI MS-9 and AEI MS-50 spectrometers. Microanalyses were performed at the Service for Microanalysis of the CNRS at Gif-sur-Yvette. Solvents were dried and purified by standard methods. All the reactions were effected under an inert atmosphere of argon. Column chromatography was carried out on silica gel 60 (0.040-0.060 mm). Preparative thin-layer chromatographic plates were laboratory-made using silica gel 60 PF_{254} (Merck).

General Procedure for the Preparation of 2-Thiothiazoline Derivatives 9a-b:

To a solution of the acid **7** (5 mmol) and oxalyl chloride (7.5 mmol) in anhydrous dichloromethane (5 ml) is added a drop of DMF. The mixture is stirred for 2 hours under argon. The solvent is then removed under reduced pressure. The crude acid chloride is added, at 0°C and in the dark, to a solution of the thiohydroxamic acid (5 mmol) and pyridine (5 mmol) in dichloromethane (10 ml). The reaction mixture is stirred for 30 minutes and filtered rapidly through silica gel (eluent dichloromethane) in the dark. The solvent is removed under reduced pressure and the product **9** is obtained pure by recrystallization.

Ester 9a: This compound formed colorless crystals (60%), m.p. 66-68 °C (from ether-pentane); $[\alpha]_D^{20}$ -260.7° (*c* 1.00, $CHCl_3$); IR (nujol) 1810, 1740 cm^{-1}; ^1H NMR (60 MHz) 1.80 (3H, d, J = 7 Hz), 2.15 (3H,s), 2.20 (3H, s),5.15 (1H, q, J = 7 Hz), 6.15 (1H, s); MS (EI, m/z): 261 $(M)^+$, 260 $(M-1)^+$, 146 $(C_4H_4NOS_2)^+$; Anal. Calcd for $C_9H_{11}NO_4S_2$: C, 41.37; H, 4.24; N, 5.36; S, 24.54 Found: C, 41.35; H, 4.29; N, 5.54; S, 24.51.

Ester 9b: This compound formed colorless crystals (85%), m.p. 80-82 °C (from ether-pentane); $[\alpha]_D^{20}$ + 23.6° (*c* 1.1, $CHCl_3$); IR (nujol) 1820, 1740 cm^{-1}; ^1H NMR (60 MHz) 2.14 (6H,s), 5.96 (2H, m), 7.48-7.06 (1H, m); MS (EI, m/z):323 $(M)^+$, 279 $(M-CO_2)^+$, 149 $(C_9H_9O)^+$; Anal. Calcd for $C_{14}H_{13}NO_4S_2$: C, 52.00; H, 4.05; N, 4.33; S, 19.83 Found: C, 51.86; H, 3.80; N, 4.47; S, 19.78.

Thermolysis of 9a:

Sulfide 10a: Compound **9a** (200 mg) was dissolved in anhydrous toluene (5 ml) and the solution refluxed for 10 min. under argon. The solvent was removed under reduced pressure and the residue chromatographed on silica gel to give the sulfide **10a** (163 mg) as a yellow oil.$[\alpha]_D^{20}$ O° (*c* 1.0, $CHCl_3$); IR (film) 1760, 1525, 1445, 1370 cm^{-1}; ^1H NMR (60 MHz) 1.63 (3H, d, J = 6Hz), 2.05 (3H, s), 2.42 (3H, m), 6.33 (1H, q, J = 6Hz); MS (EI, m/z): 218 $(M)^+$, 158 $(M-C_2H_3O_2)^+$; Anal. Calcd for $C_8H_{11}NO_2S_2$: C, 42.22; H, 5.10; N, 6.45; S, 29.51 Found: C, 44.42; H, 5.12; N, 6.45; S, 29.26.

General Procedure for the Radical Decarboxylative Addition of 9 to *N*-methylmaleimide:

A solution of **9** (1 mmol) and methylmaleimide (1.5 mmol) in anhydrous toluene was refluxed under argon for 10 minutes. The solvent was removed under reduced pressure and the residue chromatographed on silica gel (eluent ether-pentane 4:6).

Sulfide 11a: The product was obtained as a mixture of two diastereoisomers (89%).$[\alpha]_D^{20}$ O° (*c* 1.0, $CHCl_3$); IR (film) 1740, 1700 cm^{-1}; ^1H NMR (200 MHz) 1.50 (3H, d, J = 7Hz), 2.08 2.14 (3H, 2s), 2.39 (3H, s), 3.20 (3H, s), 3.43-3.58 (1H, m), 4.38 4.17 (1H, 2d, J = 6Hz), 5.80-5.54 (1H, m), 7.08 (1H, s); MS (EI, m/z): 328 $(M)^+$, 241 $(M-C_4H_7O_2)^+$; Anal. Calcd for $C_{13}H_{16}N_2O_4S_2$: C, 47.54; H, 4.91; N, 8.53; S, 19.53 Found: C, 47.58; H, 4.91; N, 8.60; S, 19.51.

Sulfide 11b: The product was obtained as a mixture of two diastereoisomers (65%). IR (film) 1750, 1700 cm^{-1}; ^1H NMR (200 MHz) 2.20 2.25 (3H, 2s), 2.39 2.38 (3H, 2s), 3.11 3.05 (3H, s), 3.78 4.03 (1H, m), 4.16 4.33 (1H, 2xd, J = 5Hz), 6.66 6.76 (1H, 2xd, J=6Hz and J= 3Hz), 7.02 7.08 (1H, 2s), 7.56-7.73 (5H, m); MS (EI, m/z): 390 $(M)^+$, 347 $(M-C_2H_3O)^+$, 241 $(M-C_9H_9O_2)^+$; Anal. Calcd for $C_{18}H_{18}N_2O_4S_2$: C, 55.37; H, 4.65; N, 7.17; S, 16.42 Found: C, 55.20; H, 4.69; N, 7.25; S, 16.40.

Radical Decarboxylation of Tartaric Acid Derivative 14 in Absence of Trap:

Sulfide 18: To a degassed solution of the 2,3-*O*-isopropylidene monomethyl tartrate **14** (500 mg, 2.45 mmol) in anhydrous THF (25 ml) was added, at -20°C and under argon, *N*-methyl morpholine (0.27 ml, 2.45 mmol) and isobutyl chloroformate (0.32 ml, 1 mmol). The mixture was stirred for 15 minutes and the sodium salt of *N*-hydroxy-2-thiopyridone (400 mg, 2.7 mmol) was added. The reaction mixture was stirred at - 20°C, in the dark, for 90 minutes, then the yellow solution irradiated with a tungsten lamp of 250 W for 30 minutes at - 20°C until the solution became colorless. The mixture was extracted with ether and washed successively with $NaHCO_3$ (0.1N), H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. Flash chromatography of the residue on silica gel (ethyl acetate-hexane 2:8) gave the the rearrangement product **18** (455 mg, 69%). It formed colorless crystals, m.p. 73 °C (from hexane); $[\alpha]_D^{20}$ -214° (*c* 0.96, $CHCl_3$); ^1H NMR (200 MHz) 1.5 (3H,s), 1.6 (3H,s), 3.8 (3H, s), 4.8 (1H, dd, J = 5 Hz), 6.6 (1H, dd, J= 5 Hz), 7.1 (1H, t, J = 6 Hz), 7.33 (1H, d, J = 8 Hz), 7.61 (1H, m), 8.56 (1H, d, J = 6 Hz); ^{13}C NMR 26.6 (CH_3), 27 (CH_3), 52.7 (CH_3), 79.9 (CH), 83 (CH), 114.2 (Cq), 120.5 (CH), 123 (CH), 136.6 (CH), 149.7 (CH), 156.9 (Cq), 169.8 (C=0); MS (EI, m/z): 269 $(M)^+$, 254 $(M-CH_3)^+$, 159 $(M-SPy)^+$; Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.51; H, 5.61; N, 5.20; S, 11.88 Found: C, 53.50; H, 5.66; N, 5.14; S, 11.92.

General Procedure for the Decarboxylative Alkylation of Tartaric acid:

To a degassed solution of the 2,3-*O*-isopropylidene monomethyl tartrate **14** (1mmol) in anhydrous THF (6 ml) was added, at -20°C and under argon, *N*-methyl morpholine (1 mmol) and isobutyl chloroformate (1 ml). The mixture was stirred for 15 minutes and the sodium salt of *N*-hydroxy-2-thiopyridone (1.1mmol) was added. The reaction mixture was stirred at - 20°C, in the dark, for 90 minutes. Then the olefin was added and the yellow solution was irradiated with a tungsten lamp of 250 W for 30 minutes at - 20°C. The mixture was extracted with ether and washed successively with $NaHCO_3$ (0.1N), H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure.

Decarboxylative Alkylation in Presence of Methyl Acrylate (5 mmol):

Flash chromatography of the residue on silica gel (ethyl acetate-hexane 8:2) gave the addition product **17a** (70%), the rearranged product **18** (2%) and the double addition product **19** (7%).

Addition product 17a : This was obtained as an oil (70%). IR (film) 1720, 1580, 1560, 1450, 1440, 1420 cm^{-1}; ^1H NMR (200 MHz) 1.3 1.4 1.6 1.7 (6H, 4s), 3.83 (3H, s), 3.9 (3H, 1s), 4.38 (1H, m), 4.50 (1H, m), 4.95 (1H, m), 7.27 (1H, m), 7.50 (1H, m), 7.80 (1H, m), 8.75 (1H, m); ^{13}C NMR 25.6 (CH_3), 35.8 36 (CH_2), 42.5 43.5 (CH), 52 52.2 (CH_3), 76.5 76.6 (CH), 78.4 78.7 (CH), 111.1 111.2 (Cq), 120 (CH), 122.3 (CH), 136.1 (CH), 149.3 (CH), 156 (Cq), 170 (C=0), 172 172.2 (C=O); MS (EI, m/z): 355 $(M)^+$, 340 $(M\text{-}CH_3)^+$, 296 $(M\text{-}CO_2CH_3)^+$; Anal. Calcd for $C_{16}H_{21}NO_6S$: C, 54.06; H, 5.95; N, 3.94; S, 9.02 Found: C, 54.06; H, 5.77; N, 3.76; S, 8.91.

Double addition product 19: This was obtained as an oil (6%); ^1H NMR (200 MHz) 1.3 to 1.6 (6H, CH_3, 6s), 2.1 to 2.3 (4H, CH_2, m), 2.9 (1H, m); 3.67 to 3.82 (9H, CO_2CH_3 m), 3.89 (1H, m), 4.26 (1H, m), 4.6 to 4.9 (1H, m), 7.12 (1H, m), 7.3 (1H, m), 7.6 (1H, m), 8.48 (1H, m); MS (EI, m/z): 441 $(M)^+$, 426 $(M\text{-}CH_3)^+$, 382 $(M\text{-}CO_2CH_3)^+$; Anal. Calcd for $C_{20}H_{27}NO_8S$: C, 54.40; H, 6.16; N, 3.17; S, 7.26 Found: C, 53.96; H, 5.87; N, 3.03; S, 6.94.

Decarboxylative Alkylation in Presence of N-methylmaleimide (1.1mmol):
Flash chromatography of the residue on silica gel (dichloromethane) gave the addition product **17b** in 93% yield as a mixture of isomers.^1H NMR (200 MHz) 1.42 1.47 1.54 (6H, 3s), 3.12 3.14 (3H, 2s), 3.48-3.64 (1H, m), 4.34 and 4.46 (1H, 2d, J= 5Hz), 4.66 and 4.95 (1H, 2dd, J_1= 8Hz, J_2= 2Hz), 4.80 and 5.40 (1H, 2d, J= 8Hz), 7.13-7.23 (1H, m), 7.37 (1H, d, J= 8Hz), 7.60-7.63 (1H, m), 8.38 (1H, d, J= 5 Hz); IR (film) 1765, 1575, 1443 cm^{-1}; MS (EI, m/z): 380 $(M)^+$, 365 $(M\text{-}CH_3)^+$, 221 $(M\text{-}C_7H_{11}O_4)^+$; Anal. Calcd for $C_{17}H_{20}N_2O_6S_2$: C, 53.67; H, 5.30; N, 7.36; S, 8.43 Found: C, 53.38. H, 5.25; N, 7.42; S, 8.48.

Decarboxylative Alkylation in Presence of Vinylsulfone (1.5 mmol):
Flash chromatography of the residue on silica gel (ethyl acetate-hexane 6:4) gave the addition product **17c** as a mixture of isomers. This was obtained as an oil; IR (film) 1750-1580-1560-1440-1405 cm^{-1}; ^1H NMR (200 MHz) 1.36 (6H, CH_3, m), 2.32 to 2.93 (2H, CH_2, m), 3.7 (3H, CH_3, s), 3.83 (3H, CH_3, s), 4.36 (2H, m), 5.96 (1H, m), 7 (2H, m), 7.43 (4H, m), 7.96 (2H, m), 8.26 (1H, m); ^{13}C NMR 26 (CH_3), 27.2 (CH_3), 32.5 (CH_2), 52.1 (CH_3), 62.4 63.5 (CH), 75.9 76.5 (CH), 77.9 79 (CH), 111.5 111.6 (Cq), 120.6 (CH), 122.4 (CH), 128.4 (CH), 129.9 (CH), 133.5 (CH), 136.3 (CH), 137.6 (CH), 149.1 (CH), 154.6 (Cq), 170.4 (C=0); MS (EI, m/z): 437 $(M)^+$, 422 $(M\text{-}CH_3)^+$; Anal. Calcd for $C_{20}H_{23}NO_6S_2$: C, 54.89; H, 5.29; N, 3.20; S, 14.65 Found: C, 54.64; H, 5.14; N, 3.12; S, 14.72.

Decarboxylative Alkylation in Presence of Ethyl Crotonate (40 mmol):
Flash chromatography of the residue on silica gel (ethyl acetate-hexane 1:9) gave the addition product **17d** as a mixture of four isomers. This was obtained as an oil (55%). ^{13}C NMR 11.3 12 12.7 13.2 14.1 (CH_3), 27.2 (CH_3), 25.6 25.9 (CH_3), 37.8 39.6 (CH), 48.7 49.6 50 50.1(CH), 52 52.3 (CH_3), 61.3 (CH_2), 76.9 77.3 78 (CH), 79.4 80 81.1 82 (CH), 111.1 111.4 (Cq), 119.8 120 (CH), 122.4 (CH), 136 136.1 (CH), 143.3 (CH), 157.2 (Cq), 171.2 171.3 171.4 171.8 (C=0), MS (EI, m/z): 384 $(MH)^+$; Anal. Calcd for $C_{18}H_{25}NO_6S$: C, 56.37; H,6.57; N, 3.65; S, 8.36 Found: C, 56.58; H, 6.49; N, 3.69; S, 8.35.

Decarboxylative Alkylation in Presence of Crotononitrile (40mmol):

Flash chromatography of the residue on silica gel (ethyl acetate-hexane 3:7) gave the addition product **17e** as a mixture of isomers. This was obtained as an oil (25%). IR (film) 2220, 1750, 1580, 1560, 1450, 1405 cm^{-1}; ^1H NMR (200 MHz) 1.36 (9H, CH_3, m), 2.26 (1H, CH, m), 3.6 (3H, CH_3, 2s), 4.36 (2H, CH, s), 5.16 (0.5 d, J= 7Hz), 5.4 (1H, d, J = 5 Hz), 7.06 (1H, m), 7.2 (1H, m), 7.56 (1H, m), 8.46 (1H, m),; MS (EI, m/z): 337 $(MH)^+$, 228 $(MH\text{-}SPy)^+$; Anal. Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.32; S, 9.53 Found: C, 56.87; H, 6.20; N, 8.44; S, 9.32.

Decarboxylative Alkylation in Presence of Methylvinysulfone (10mmol):

Flash chromatography of the residue on silica gel (ethyl acetate-hexane 3:7) gave the addition product **17f** as a mixture of isomers. This was obtained as an oil (13%). ^{13}C NMR 12.1 12.9 14.3 15.2 (CH_3), 25.6 25.8 26 (CH_3), 26.6 26.9 27.3 27.5 (CH_3), 33.7 35.2 36.2 36.9 (CH), 52.2 52.3 (CH_3), 66.2 66.8 67.7 67.9 (CH), 76.1 77.4 78.6 (CH), 79.9 80.8 81 82 (CH), 111.3 111.8 (Cq), 120.4 120.5 (CH), 122.1 122.3 (CH), 127.9 128.1 128.2 (CH), 129.4 129.5 129.7 (CH), 133.5 133.7 (CH), 136 136.2 (CH), 137.4 137.8 (Cq), 148.7 148.8 (CH), 153.9 (Cq), 171.3 (C=0); MS (EI, m/z): 452 $(MH)^+$, 393 $(MH\text{-}SPy)^+$, 255 (M393- $HSO_2Ph)^+$.

General Procedure for the Photolysis of 24 in Presence of Olefins 16e-g:

To a degassed solution of the adamatyl derivative **24** (1mmol) in anhydrous THF (6 ml) was added, at 0°C and under argon the olefin and the yellow solution irradiated with a tungsten lamp of 250 W for 1 hour at 0°C. The solvent was removed under reduced pressure

Decarboxylative Alkylation in Presence of Methyl Crotonate (30 mmol):

Flash chromatography of the residue on silica gel (ethyl acetate-hexane 0.5:9.5) gave the addition product **25g** as a mixture of two diastereoisomers (48%) which partially separate. *The less polar:* This was obtained as an oil .IR (film) 1720, 1580, 1440, 1405 cm^{-1}; ^1H NMR (200 MHz) 1.16 (3H, d, J= 7Hz), 1.66 (12H, m); 1.96 (4H, m), 3.73 (3H, s), 5.03 (1H, d, J= 4Hz), 7 (1H, m), 7.2 (1H, d, J= 7Hz), 7.5 (1H, t, J= 7 Hz), 8.46 (1H, d, J= 5 Hz); ^{13}C NMR 10.2 (CH_3), 28.8 (CH_2) 36.9 (Cq), 37.1 (CH), 39.7 (CH), 46.7 (CH_3), 47.3 (CH), 51.6 (Cq), 119.6 (CH), 122 (CH), 135.9 (CH), 143.9 (CH), 157.9 (Cq), 172.6 (C=O); MS (EI, m/z): 345 $(MH)^+$; Anal. Calcd for $C_{20}H_{27}NO_2S$: C, 69.52; H, 7.87; N, 4.05; S, 9.28 Found: C, 69.57; H, 7.80; N, 3.86; S, 8.87. *The more polar:* This was obtained as an oil .IR (film) 1720, 1580, 1440, 1405 cm^{-1}; ^1H NMR (200 MHz) 1.06 (3H, d, J= 7Hz), 1.66 (12H, m); 1.96 (4H, m), 3.73 (3H, s), 4.96 (1H, d, J= 3Hz), 7 (1H, m), 7.23 (1H, d, J= 7Hz), 7.5 (1H, t, J= 7 Hz), 8.43 (1H, d, J= 5 Hz); ^{13}C NMR 10.7 (CH_3), 28.7 (CH_2) 35.7 (Cq), 37 (CH), 39.9 (CH), 44.9 (CH_3), 47.9 (CH), 52.1 (Cq), 119.2 (CH), 122 (CH), 135.6 (CH), 149.1 (CH), 157.9 (Cq), 173.8 (C=O); MS (EI, m/z): 345 $(MH)^+$; Anal. Calcd for $C_{20}H_{27}NO_2S$: C, 69.52; H, 7.87; N, 4.05; S, 9.28 Found: C, 69.43; H, 7.88; N, 4.20; S, 9.27.

Decarboxylative Alkylation in Presence of Crotononitrile (20mmol):

Flash chromatography of the residue on silica gel (ethyl acetate-hexane 0.5:9.5) gave the addition product **25e**. This was obtained as an oil (51%). IR (film) 2220, 1580 cm^{-1}; ^1H NMR (200 MHz) 1.2 (3H, d, J= 7 Hz), 1.6 to 2.1 (16H, m), 5.33 (1H, d, J = 1 Hz), 7.06 (1H, m), 7.2 (1H, d, J = 8 Hz), 7.56 (1H, t, J = 8 Hz), 8.5

(1H, d, J = 5 Hz); ^{13}C NMR 11.1 (CH_3), 28.6 (CH_2) 33 (CH), 36.1 (Cq), 37 (CH), 39.7 (CH), 47.4 (CH), 119.4 (CN), 120.6 (CH), 122.3 (CH), 136.5 (CH), 149.6 (CH), 155.2 (Cq); MS (EI, m/z): 312 $(M)^+$, 242 $(M\text{-}SPy)^+$; Anal. Calcd for $C_{19}H_{24}N_2S$: C, 73.02; H, 7.74; N, 8.96; S, 10.26 Found: C, 73.30; H, 7.65; N, 8.69; S, 10.49.

Decarboxylative Alkylation in Presence of Methylvinysulfone (10mmol):
Flash chromatography of the residue on silica gel (ethyl acetate-hexane 1:9) gave the addition product **25f** as a white solid (14%). IR (film) 1560, 1450, 1400, 1360, 1140 cm^{-1}; ^1H NMR (200 MHz) 1.2 (3H, d, J= 7 Hz), 1.6 (11H, m), 1.9 (4H, s), 2.4 (1H, q, J = 7 Hz), 6.26 (1H, s), 6.9 (2H, m), 7.3 (4H, m), 7.9 (2H, d, J = 8 Hz), 8.2 (1H, d, J = 8 Hz); MS (EI, m/z): 428 $(MH)^+$, 319 $(MH\text{-}HSPy)^+$; Anal. Calcd for $C_{24}H_{29}N_2O_2S_2$: C, 67.40; H, 6.83; N, 3.27; S, 14.99 Found: C, 67.24; H, 6.99; N, 3.43; S, 14.80.

General Procedure for the Oxydation-Elimination of the Thiothiazolyl and Thiopyridyl Groups:

To a solution of the addition product (1 mmol) in $CHCl_3$ (5 ml) was added metachloroperbenzoic acid (1.2 mmol) at 0°C. The reaction mixture was stirred one hour at O°C. The solution was then diluted with dichloromethane and washed successively with $NaHCO_3$ (0.1N), H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude sulfoxide was taken up in anhydrous toluene (5 ml) and the solution was refluxed for 30 minutes. The solvent was then removed under reduced pressure and the residue flash chromatographed on silica gel.

N-methylmaleimide Derivative 13: This was obtained as an oil (76%). IR (film) 1700, 1440, 1240 cm^{-1}; ^1H NMR (60 MHz) 1.54 (3H, d, J = 7Hz), 2.15 (3H, m), 3.02 (3H, s), 5.90-5.50 (1H, m), 6.40 (1H, d, J=2Hz); MS (EI, m/z): 197 $(M)^+$, 155 $(M\text{-}C_2H_2O)^+$; Anal. Calcd for $C_9H_{11}NO_3$: C, 54.82; H, 5.62; N, 7.10 Found: C, 54.83; H, 5.45; N, 7.10.

Methylacrylate Derivative 20a: Flash chromatography of the residue on silica gel (ethyl acetate-hexane 2:8) gave the olefin (75%).This was obtained as an oil. $[\alpha]_D^{20}$ -35° (*c* 2.21, $CHCl_3$); ^1H NMR (200 MHz) 1.5 (6H, s), 3.8 (3H, s), 3.9 (3H, s), 4.35 (1H, d, J = 8 Hz), 4.8 (1H, m, J_1 = 8 Hz, J_2 = 5 Hz), 6.28 (1H, dd, J_1 = 16 Hz, J_2 = 2 Hz), 7.1 (1H, dd, J_1 = 16 Hz, J_2 = 5 Hz); ^{13}C NMR 25.5 (CH_3), 25.7 (CH_3), 51.5 (CH_3), 52.3 (CH_3), 77.4 (CH), 78.4 (CH), 111.9 (Cq), 122.3 (CH), 143 (CH), 165.9 (C=O), 169.7 (C=O); MS (EI, m/z): 244 $(M)^+$, 229 $(M\text{-}CH_3)^+$, 185 $(M\text{-}CO_2CH_3)^+$, Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.66 Found: C, 54.09; H, 6.61.

N-methylmaleimide Derivative 20b: Flash chromatography of the residue on silica gel (ether-pentane 1:1) gave the olefin (52%). This was obtained as an oil. $[\alpha]_D^{20}$ -3.5° (*c* 0.86, $CHCl_3$); b.p. 180°C/ 0.3 mmHg (Kugelrohr); IR (film) 1760, 1715 cm^{-1}; MS (EI, m/z): 254 $(M)^+$; ^1H NMR (400 MHz) 1.33 (3H, s), 1.45 (3H, s), 2.48 (3H, s), 3.43 (3H, s), 4.36 (1H, d, J = 7 Hz), 5.14 (1H, d, J = 7 Hz), 6.17 (1H, s). MS (EI, m/z): 254 $(M)^+$; Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.61; N, 5.20 Found: C, 53.34; H, 5.72; N, 4.93.

*Vinylsulfone Derivative **20c**:* Flash chromatography of the residue on silica gel (ethyl acetate-hexane 2:8) gave the olefin (64%) . This was obtained as a colourless crystalline compound; m.p. 52 °C (from dichoromethane-hexane); $[\alpha]_D^{20}$ -29° (*c* 1.00, $CHCl_3$); ^1H NMR (200 MHz) 1.43 (6H, CH_3, s), 3.83 (3H, CH_3, s), 4.33 (1H, d, J = 8 Hz), 4.8 (1H, m), 6.75 (1H, d, J = 15 Hz), 7.13 (1H, dd, J_1 = 4 Hz, J_2 = 15 Hz), 7.63 (3H, m), 7.93 (2H, m); ^{13}C NMR 25.8 (CH_3), 26.6 (CH_3), 52.6 (CH_3), 76.5 (CH), 78.2 (CH), 112.4 (Cq), 127.7 (CH), 129.3 (CH), 132.5 (CH), 133.6 (CH), 139.9 (CH), 140.9 (CH), 169.4 (C=0); MS (EI, m/z): 327 $(MH)^+$; Anal. Calcd for $C_{15}H_{18}O_6S$: C, 55.19; H, 5.55; S, 9.82 Found: C, 54.95; H, 5.36; S, 10.03.

*Ethyl Crotonate Derivative **20d**:* Flash chromatography of the residue on silica gel (ethyl acetate-hexane 3:7) gave the olefin (70%) as a mixture of E and Z isomers. This was obtained as an oil. ^1H NMR (200 MHz) 1.26 (6H, CH_3, q, J = 7 Hz), 1.5 (12H, CH_3, m), 1.95 (3H, CH_3, s), 3.73 (3H, CH_3, s), 3.83 (3H, CH_3, s), 4.16 (4H, m), 4.3 (1H, d, J = 8 Hz), 4.66 (1H, d, J = 7 Hz), 5.9 (1H, s), 6.03 (1H, s); ^{13}C NMR 13.6 (CH_3), 17.9 (CH_3), 25.2 25.3 (CH_3), 26.1 26.2 (CH_3), 51.7 51.9 (CH_3), 59.3 59.4(CH_2), 75.6 76.5 (CH), 77.8 82.1 (CH), 111.4 111.7 (Cq), 118 120.1 (CH), 151.8 152.1 (CH), 164.6 165.6 (C=0), 169.9 170.2 (C=0); MS (EI, m/z): 272 $(M)^+$; 257 $(M\text{-}CH_3)^+$; Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.33; H,7.40 Found: C, 57.63; H, 7.65.

*Crotononitrile derivative **20e**:* Flash chromatography of the residue on silica gel (ethyl acetate-hexane 1:1) gave the olefin (50%) as a single isomer. This was obtained as an oil.^1H NMR (200 MHz) 1.55 (6H, CH_3, 2s), 2.1 (CH_3, s), 3.83 (3H, CH_3, s), 4.1 (1H, d, J = 7 Hz), 4.7 (1H, d, J= 7 Hz), 5.6 (1H, d, J = 1 Hz), ^{13}C NMR 16.8 (CH_3), 25.6 (CH_3), 52.7 (CH_3), 78.2 (CH), 80.6 (CH), 97.2 (CH), 112.6 (Cq), 116.1 (CN), 159.2 (Cq), 170.3 (C=0), MS (EI, m/z):225 $(M)^+$.

General Procedure for the Reductive Elimination of the Thiopyridyl Group:

To a solution of the addition product (1mmol) in absolute ethanol (5 ml) is added Raney Nickel (2g) and the mixture was refluxed for one hour. The suspension is filtered through celite and the solvent removed under reduced pressure. The residue was then flash chromatographed on silica gel.

*Methyl Acrylate Derivative **26a**:* Flash chromatography of the residue on silica gel (dichloromethane) gave the product (84%).This was obtained as an colorless oil. $[\alpha]_D^{20}$ -15.53° (*c* 1.39, $CHCl_3$); b.p. 150°C/0.2 mmHg (Kugelrorh); IR (film) 1780, 1750 cm^{-1}; ^1H NMR (400 MHz) 1.43 (3H, s), 1.46 (3H, s), 2.02-1.92 (1H, m), 2.23-2.13 (1H, m), 2.55-2.46 (2H, m), 3.72 (3H, s), 3.79 (3H, s), 4.16 (2H, m); MS (EI, m/z): 246 $(M)^+$, 245 $(M\text{-}H)^+$, 231 $(M\text{-}CH_3)^+$; Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37 Found: C, 53.88; H, 7.26.

*Ethyl Crotonate Derivative **26d**:* Flash chromatography of the residue on silica gel (ethyl acetate-hexane 3:7) gave the product (80%) as a mixture of isomers. This was obtained as an oil. ^1H NMR (200 MHz) 1.0 (3H, CH_3, d, J = 7 Hz), 1.25 (3H, CH_3, t, J = 7Hz), 1.4 (3H, CH_3, s), 3.44 (3H, CH, CH_2, m), 3.8 (3H, CH_3, s), 4.16 (3H, CH, CH_2, s), 4.3 (1H, m); ^{13}C NMR 13.9 14 (CH_3), 15.8 (CH_3), 25.3 25.4 (CH_3), 26.5 26.7 (CH_3), 32.1 33.5 (CH_2), 37.1 37.9 (CH_2), 52 (CH_3), 60 (CH_2), 76.2 76.3 (CH), 81.5 82.3 (CH), 110.8

110.9 (Cq), 171.3 171.4 (C=0), 172 172.2 (C=0); MS (EI, m/z): 273 $(M-1)^+$; 259 $(M-CH_3)^+$, 229 $(M-OEt)^+$; Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.91; H, 8.08 Found: C, 56.73; H, 7.89.

Treatment of the Olefin 20 with RuO_4 and CH_2N_2

To a suspension of ruthenium dioxide (5 mg) in a mixture of acetone-water (30 ml, 1:1) was added sodium metaperiodate (5 mmol). This solution is then added to the olefin **20** (544 mg, 2.23 mmol) in acetone (10 ml). The mixture was stirred for 30 minutes then filtered through celite and the acetone was removed under reduced pressure at 20°C. The residue was taken up in ether and washed two times with brine. The organic layer was dried over $MgSO_4$ and the solvent evaporated to dryness under reduced pressure at 20°C. The residue was dissolved in acetonitrile (10 ml) and an ethereal solution of diazomethane was added at 0°C until persistence of the yellow color. The excess of reagent was then destroyed with a small amount of acetic acid. The solvent was removed under reduced pressure and the residue chromatographed on silica gel to give the dimethyl 2,3-isopropylidene tartrate **21** (330 mg, 68%) as a colorless oil . The spectroscopic data of the compound and the physical properties were identical to an authentic sample prepared according to the litterature procedure[18]. b.p. 85 °C (0.15 mmHg); $[\alpha]_D^{20}$ -58° (*c* 0.86, MeOH); ^1H NMR (80 MHz) 1.50 (6H, s), 3.80 (6H,s), 4.75 (2H, s); ^{13}C NMR 26.3 (CH_3), 52.7 (CH_3), 77.1 (CH), 113.9(CHq), 170.1 (C=O); Anal. Calcd for $C_9H_{14}O_6$: C, 49.53; H, 6.46 Found: C, 49.73; H, 6.43.

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