Bull Soc Chim Fr (1997) 134, 703-711

En route to an efficient preparation of biocartol esters. Synthetic and structural investigations in the (1*R*,3*S*)-(−)-2,2-dimethyl-3-formylcyclopropane-1-carboxylic acid series

Marc Veyrat[1], Laurence Fantin[1], Serge Desmoulins[1], Anne Petitjean[1], Marinella Mazzanti[1], René Ramasseul[1], Jean-Claude Marchon[1]*, Robert Bau[2]

[1] *Département de Recherche Fondamentale sur la Matière Condensée, Service de Chimie Inorganique et Biologique, Laboratoire de Chimie de Coordination*†, *CEA-Grenoble, 38054 Grenoble, France*
[2] *Department of Chemistry, University of Southern California, Los Angeles, California 90089-0744, USA*

(Received 7 April 1997; accepted 2 July 1997)

Summary — Enantiopure esters are obtained in good yield from (1*R*,3*S*)-(−)-2,2-dimethyl-3-formylcyclopropane-1-carboxylic acid (biocartol) in three steps: (1) dithiane protection of the aldehyde function; (2) esterification of the carboxylic acid function; (3) dethioketalization. The X-ray structures of biocartol and of its acetal 'dimer' are reported.

chrysanthemic acid / biocartol / chiroporphyrin / stereochemistry

Résumé — **Vers une préparation efficace d'esters du biocartol. Études synthétiques et structurales dans la série de l'acide (1*R*,3*S*)-(−)-2,2-diméthyl-3-formylcyclopropane-1-carboxylique.** À partir de l'acide (1*R*,3*S*)-(−)-2,2-diméthyl-3-formylcyclopropane-1-carboxylique (biocartol) on obtient avec un bon rendement des esters énantiopurs en trois étapes: (1) protection de la fonction aldéhyde par un dithiane; (2) formation de l'ester; (3) déprotection. Les structures aux rayons X du biocartol et de son dérivé 'dimère' sont décrites.

acide chrysanthémique / biocartol / chiroporphyrine / stéréochimie

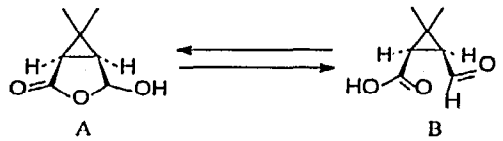
Introduction

The search for efficient routes to the esters derived from the tautomeric form (1*R*,3*S*)-(−)-2,2-dimethyl-3-formylcyclopropane-1-carboxylic acid **B** of (1*R*)-*cis*-caronaldehydic acid hemiacetal **A** (also called (1*R*)-*cis*-hemicaronaldehyde, (1*R*)-*cis*-caronaldehyde, or biocartol) has been a topic of great interest for the synthesis of pyrethroid insecticides in the last decade [1]. Recently, these esters have found promising use as synthons for the preparation of asymmetric metalloporphyrin catalysts bearing chiral cyclopropyl groups on the four *meso* positions [2]. In the present investigation, we have reexamined two published procedures for the preparation of some of these esters: the acid-catalyzed reaction of alcohols with form **A** of biocartol [3], and the corresponding process induced by *N*,*N*′-dicyclohexylcarbodiimide/4-(dimethylamino)pyridine (DCC/DMAP) described in the patent literature [4]. Finally, we report on a third procedure, which involves dithiane protection of the aldehyde function, and is satisfactory in terms of both the yield and the stereochemical purity of the desired esters.

Results and discussion

Acid-catalyzed esterification

^{1}H NMR indicates that at room temperature biocartol is in equilibrium between closed **A** and open **B** forms in chloroform solution [5]:

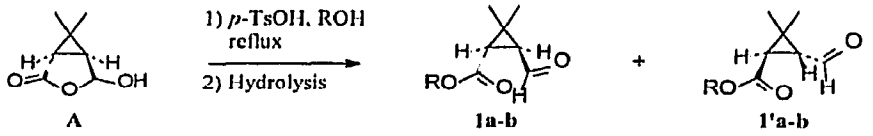


Scheme 1

In our hands, the acid-catalyzed esterification gave rise to slight epimerization of the asymmetric center bearing the aldehyde function. Reaction of **A** [6] with methanol or ethanol induced by *p*-toluenesulfonic acid followed by acid treatment of the ketal intermediate gave ester **1a,b** in 40–60% yield after chromatography (scheme 2). The presence of an epimeric (1*R*)-*trans* ester **1′a,b** is observed in both cases (**1′a**, R = Me, yield 1%,

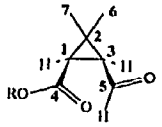
* Correspondence and reprints

† Unité de Recherche Associée au CNRS n° 1194



Scheme 2

Table I. ^{1}H NMR data (δ ppm[a]) in $CDCl_3$ of compounds **1a–g**, **3**, **4** and **B** containing the open biocartol moiety:



Compound	*H_1 (d)*	*$J_{1,3}$*	*H_3 (dd)*	*H_5 (d)*	*$J_{3,5}$*	*H_6 or H_7 (s)*		*Other protons (R group)*
1a	2.13	8.7	1.74	9.76	6.2	1.25	1.53	3.71 (s, 3H, CH_3)
1b	2.09	8.7	1.80	9.71	6.4	1.30	1.52	4.16 (q, 2H, CH_2, 6.6 Hz); 1.21(t, 3H, CH_3, 6.6 Hz)
1c	2.16	8.7	1.83	9.74	6.4	1.24	1.53	5.12 (s, 2H, CH_2); 7.34 (m, 5H, arom)
1d	2.14	8.8	1.83	9.73	6.4	1.29	1.54	3.79 (s, 2H, CH_2); 0.91 (m, 9H, CH_3)
1e	2.36	8.6	2.05	9.75	6.0	1.37	1.61	7.29 (d, 2H, 9.1 Hz, H arom) 8.26 (d, 2H, 9.1 Hz, H arom)
1f	2.39	8.6	2.05	9.80	6.0	1.38	1.63	7.46 (dd, 1H, 8.1 Hz, 2 Hz) 7.54–8.00 (m, 2H, H arom) 8.11 (dd, 1H, 8.1 Hz, 2 Hz, H arom)
1g	2.08	8.0	1.72[b]	9.65	6.4	1.22	1.47	0.75 (s, 3H, Me borneol); 0.78 (s, 3H, Me borneol) 0.81 (s, 3H, Me borneol); 0.90 (m, 1H, H borneol) 1.17 (m, 1H, H borneol); 1.72 (bb, 5H, H borneol) 4.85 (m, 1H, CH–O–C(O))
3[b]	2.12	8.6	1.91	9.73	6.3	1.28	1.53	See table III
4[c]	2.27	8.6	1.77	9.61	6.2	1.26	1.43	1.14–1.27 (broad m and 1s, 8H and 3H, cyclohexyl protons and Me) 1.66–1.96 (broad m and 1dd, 12H and 1H, cyclohexyl protons and H_3); 3.60 (m, 1H, N–CH) 3.88 (tt, 1H, 3.3 Hz, 11.9 Hz, N–CH_{ax}); 7.24 (m, NH)
B[c]	2.14	8.5	1.31	9.71	6.2	1.29	1.56	

At 200 MHz unless specified otherwise; [a] $CHCl_3$ ref: 7.24 ppm; [b] 300 MHz; [c] 400 MHz.

$J_{1,3}$ = 5.6 Hz, $J_{3,5}$ = 3.6 Hz, cf table I; **1'b**, R = Et, yield 7%).

DCC/DMAP-catalyzed esterification

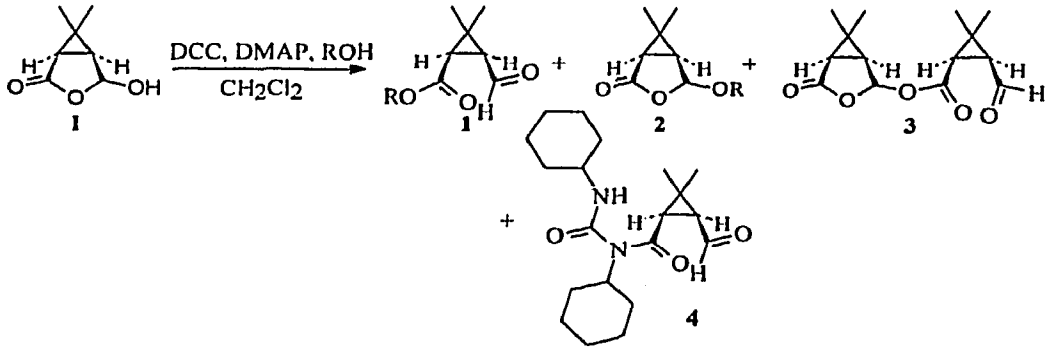
In the presence of DCC/DMAP [7a–d] reaction of **A** with methanol, ethanol, or benzyl alcohol gave the stereochemically pure (1*R*)-*cis* esters **1a–c** albeit in moderate yield (ca 20–40%) after column chromatography (scheme 3). With neopentyl alcohol, the ester **1d** was obtained in only 5% yield but free of the *trans* epimer, while no product formation was observed with *p*-nitrophenol. Three side-products **2**, **3** and **4** were present in the crude reaction mixture for each investigated alcohol.

Acetal isomers **2a–d** of the desired esters **1a–d** most likely derive from the bicyclic form **A** of biocartol [7e]. We did not try to isolate any symmetric ether (ROR) that may be formed from the respective alcohol. Two side-products, biocartol 'dimer' **3** and *N*-acylurea **4**, are common to all investigated reactions. The latter is very likely a condensation product of the open form **B** and DCC. It has been reported by Keck et al that under high dilution conditions, the DCC/DMAP-catalyzed esterification leads to the formation of a substantial amount of *N*-acylurea [8]. Thus, the unexpectedly high relative abundance of **4** in the present experiments may be due to the low equilibrium concentration of the open form **B**.

Proton and carbon NMR resonance assignments of esters **1a–e** (tables I and II) and acetals **2a–d** (tables III and IV) are in full agreement with previous work [9]. They also allow proton and carbon resonance attributions to be made for biocartol **A**, its 'dimer' **3**, and the urea derivative **4**. The ^{1}H NMR spectra of the bicyclic compounds **A**, **2a–c**, and **3** (table III) show similar patterns and share common characteristics, particularly a small value (0.8 Hz) of the coupling constant $J_{3,5}$ between the cyclopropyl proton H_3 and the ketal proton H_5 (scheme 4), suggesting that these are nearly perpendicularly oriented. The methylene protons of the OR group in **2b–d** are diastereotopic, as indicated for example by the highly complex multiplet observed for this group in **2b**.

X-ray crystallography of biocartol A and its 'dimer' 3

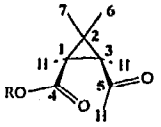
The structures assigned to compounds **A** and **3** on the basis of their ^{1}H and ^{13}C NMR spectra were confirmed by X-ray diffraction (tables V–VII). The structures of



R	*Me*	*Et*	*Bz*	*Np*	*p-C6H4NO2*
Ester	**1a**	**1b**	**1c**	**1d**	**1e**
Acetal	**2a**	**2b**	**2c**	**2d**	**2e**

Scheme 3

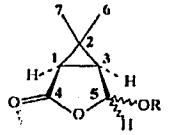
Table II. ^{13}C NMR data (δ ppm[a]) in $CDCl_3$ of compounds **1a–e**, **3**, **4** and **B** containing the open biocartol moiety:



Compound	*C1*	*C2*	*C3*	*C4*	*C5*	*C6 or C7*		*Other carbons*
1a	36.0	29.7	40.8	170.3	200.8	15.0	28.2	52.1 OCH_3
1b	36.1	29.4	40.5	171.6	200.2	14.7 or 15.0	27.9	66.8 OCH_2; 14.7 or 15.0 CH_3
1c	36.0	29.7	40.7	169.5	199.9	14.7	28.0	66.8 OCH_2; 135.4 C arom; 128.1 128.2 128.4 CH arom
1d	36.2	29.4	40.7	171.0	200.2	14.9	28.1	74.4 OCH_2; 26.3 CH_3 (*t*Bu); 31.1 C (*t*Bu)
1e	35.2	30.9	41.2	167.5	198.9	14.7	28.0	122.3 125.1 CH arom, 145.5 155.0 C arom
3[b]	34.4	30.4	41.0	168.1	198.9	14.7	28.0	See table IV
	35.1			171.7				
4[b]	40.0	29.2	40.0	169.5	200.0	15.5	27.2	24.5 24.6 25.1 25.3 26.3 CH_2
	41.2		41.2					26.4 30.8 30.9 32.5 32.7 CH_2
								40.0 41.2 CH; 153.3 C (urea)
B[c]	35.6		41.0			14.8	28.1	

At 50 MHz unless specified otherwise; [a] $CDCl_3$ ref: 76.9 ppm; [b] 75 MHz; [c] 100 MHz.

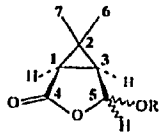
Table III. ^1H NMR data (δ ppm[a]) in $CDCl_3$ of compounds **2a–d**, **3** and **A** containing the closed biocartol moiety:



Compound	*H1 (d)*	*J1,3*	*H3 (dd)*	*H5 (d)*	*J3,5*	*H6 or H7 (s)*		*Other protons (R group)*
2a	2.01	5.7	1.98	5.02	< 1	1.13	1.16	3.48 (s, 3H, CH_3)
2b	2.05	5.7	2.02	5.14	< 1	1.16	1.19	1.24 (t, 3H; CH_3, 7.0 Hz)
								3.59 (m, 1H); 3.87 (m, 1H)
2c	2.06	5.7	2.03	5.22	0.8	1.15	1.17	4.61 (d, 1H, 11.5 Hz)
								4.89 (d, 1H, 11.5 Hz)
								7.34 (s, 5H, H arom)
2d	1.98	5.9	2.03	5.59	4.0	1.14	1.23	0.93 (s, 9H, CH_3)
								3.15 (d, 1H, 8.6 Hz)
								3.45 (d, 1H, 8.6 Hz)
3[b]	2.08	5.6	2.14	6.28	< 1	1.18	1.21	See table I
A[c]	2.08	5.6	2.05	5.46	0.8	1.16	1.17	4.02 (m, OH)

At 200 MHz unless specified otherwise; [a] $CHCl_3$ ref: 7.24 ppm; [b] 300 MHz; [c] 400 MHz.

Table IV. ^{13}C NMR data (δ ppm[a]) in $CDCl_3$ of compounds **2a,c, 3** and **A** containing the closed biocartol moiety:

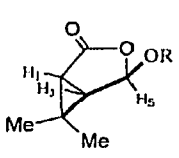


Compound	C_1	C_2	C_3	C_4	C_5	C_6 *or* C_7		*Other carbons*
2a	35.1	24.3	29.8	173.1	102.3	14.9	25.2	56.1 OCH_3
2c	35.3	24.6	29.9	173.5	100.2	15.0	25.3	70.5 OCH_2 136.3 C arom 128.1 128.3 128.5 CH arom
3[b]	34.4 35.15	25.1	29.0	168.1 171.7	92.9	14.7	25.2	See table II
A[c]	36.4	24.8	30.2	173.5	96.0	14.9	24.8	

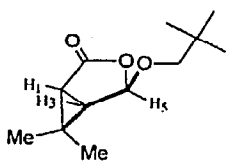
At 50 MHz unless specified otherwise; [a] $CDCl_3$ ref: 76.9 ppm; [b] 75 MHz; [c] 100 MHz.

Table V. Summary of crystal data, data collection parameters and structure refinement for biocartol **A** and its 'dimer' **3**.

Compound	*Biocartol A*	*Biocartol 'dimer' 3*
Crystal data		
Emp formula; M (g/mol)	$C_7H_{10}O_3$; M = 142.15	$C_{14}H_{18}O_5$; M = 266.29
Color; habit	Colorless prism	Colorless prism
Crystal size (mm)	0.14 × 0.22 × 0.36	0.24 × 0.36 × 0.46
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2(1)2(1)2(1)$ (# 19)	$P2(1)2(1)2(1)$
Lattice parameters	a = 7.321(1) Å	a = 6.3003(9) Å
(or unit cell dimension)	b = 7.445(1) Å	b = 11.202(2) Å
	c = 13.613(3) Å	c = 19.558(3) Å
	α = 90°	α = 90°
	β = 90°	β = 90°
	γ = 90°	γ = 90°
Volume	742.0(2) $Å^3$	1380.3(3) $Å^3$
Z	4	4
Density calc (g/cm^3)	1.273	1.281
Absorption coefficient	μ(CuKα) 0.834 mm^{-1}	μ(MoKα) 0.97 cm^{-1}
F(000)	304	568
Data collection		
2θ range	2.0 to 105.0°	2.0 to 50.0°
Scan type	ω	ω
Scan speed (in ω)	8.0°/min (up to 3 scans)	8.0°/min (up to 3 scans)
Reflections collected	1332	1998
independent reflections	814 (R_{int} = 0.0288)	1455 (R_{int} = 0.035)
Observed reflections	814 ($I > 2\sigma(I)$)	912 ($I > 3\sigma(I)$)
Solution and refinement		
Solution	Direct methods	Direct methods
Refinement methods	Full matrix least-squares on F^2	Full matrix least-squares on F^2
Quantity minimized	$\Sigma\omega(\|F_o\| - \|F_c\|)^2$	$\Sigma\omega(\|F_o\| - \|F_c\|)^2$
Final R indices	R = 3.38%, wR = 9.91% ($I > 2\sigma(I)$)	R = 4.0%; wR = 4.0% ($I > 3\sigma(I)$)
Goodness of fit	1.09	1.39
Data-to-parameter ratio	814:102	912:173
Largest difference peak	0.120 e $Å^{-3}$	0.15 e $Å^{-3}$
Largest difference hole	−0.106 e $Å^{-3}$	−0.17 e $Å^{-3}$



A, 2a-c, 3



2d

Scheme 4

A and **3**, shown in figures 1 and 2, reveal a common feature. The hydroxyl substituent of the five-membered ring is in *exo* configuration, implying *R*-absolute configuration of carbon C_5 for both compounds.

As suggested above, the small value of $J_{3,5}$ for **A** and **3** in solution is consistent with a dihedral angle $H_3C_3C_5H_5$ close to 90°. This implies that the *R* configuration of C_5, which is observed for **A** and **3** in the crystal, is retained in solution. A similar conclusion

Table VI. Atomic coordinates (Å × 10^4) and isotropic displacement parameters (Å^2) for (1*R*)-*cis*-caronaldehydic acid hemiacetal **A** (biocartol).

	x	*y*	*z*	*U (eq)*
C(1)	5598(4)	568(4)	7109(2)	44(1)
C(2)	7179(4)	1803(4)	6945(2)	40(1)
C(3)	7557(4)	−101(4)	7151(2)	46(1)
C(4)	4673(4)	449(4)	6165(2)	42(1)
C(5)	7107(4)	2394(4)	5895(2)	41(1)
C(6)	8302(5)	−1349(5)	6382(3)	65(1)
C(7)	8217(5)	−511(5)	8192(3)	71(1)
O(8)	3232(3)	−283(3)	5964(2)	59(1)
O(9)	5606(3)	1331(3)	5464(1)	46(1)
O(10)	6685(3)	4188(3)	5816(1)	55(1)

Table VII. Atomic coordinates (Å) and isotropic displacement parameters (Å^2) for biocartol dimer **3**.

Atom	*x*	*y*	*z*	B_{eq}[a]
O(8)	−0.1257(7)	−0.0915(3)	−0.6852(2)	5.43(10)
O(9)	0.0609(5)	0.0344(3)	−0.7502(2)	3.62(8)
O(10)	0.0129(5)	0.0796(3)	−0.8642(1)	3.01(7)
O(18)	0.3665(6)	0.1080(3)	−0.8744(2)	4.84(10)
O(19)	0.6901(7)	−0.1418(3)	−0.9724(2)	6.5(1)
C(1)	−0.2916(7)	0.0840(4)	−0.7319(2)	3.1(1)
C(2)	−0.2023(8)	0.1741(4)	−0.7812(2)	3.1(1)
C(3)	−0.2478(7)	0.2129(4)	−0.7095(2)	3.0(1)
C(4)	−0.1228(9)	−0.0024(4)	−0.7187(2)	3.6(1)
C(5)	0.0177(8)	0.1312(4)	−0.7966(2)	3.0(1)
C(6)	−0.0791(9)	0.2401(4)	−0.6588(2)	3.9(1)
C(7)	−0.4433(8)	0.2877(5)	−0.7008(2)	4.5(1)
C(11)	0.2036(8)	0.0675(4)	−0.8966(2)	3.0(1)
C(12)	0.1695(7)	0.0020(4)	−0.9611(2)	3.0(1)
C(13)	0.2491(8)	0.0467(4)	−1.0293(2)	3.7(1)
C(14)	0.3570(8)	−0.0609(4)	−0.9978(2)	3.6(1)
C(15)	0.5737(8)	−0.0569(5)	−0.9714(3)	4.1(1)
C(16)	0.3702(9)	0.1643(5)	−1.0338(3)	4.9(1)
C(17)	0.1087(9)	0.0251(6)	−1.0896(2)	5.7(2)
H(20)	−0.4360	0.0575	−0.7349	3.0000
H(21)	−0.2805	0.2116	−0.8181	3.0000
H(22)	0.1327	0.1895	−0.7986	3.0000
H(23)	0.0588	0.2045	−0.6574	3.0000
H(24)	−0.0258	0.3194	−0.6647	3.0000
H(25)	−0.1264	0.2300	−0.6109	3.0000
H(26)	−0.3990	0.3689	−0.7057	3.0000
H(27)	−0.5306	0.2771	−0.6601	3.0000
H(28)	−0.5457	0.2814	−0.7366	3.0000
H(29)	0.0498	−0.0481	−0.9685	3.0000
H(30)	0.3068	−0.1396	−1.0087	3.0000
H(31)	0.6450	0.0197	−0.9653	3.0000
H(32)	0.2988	0.2399	−1.0395	3.0000
H(33)	0.4819	0.1850	−1.0023	3.0000
H(34)	0.4629	0.1487	−1.0721	3.0000
H(35)	0.1842	0.0220	−1.1311	3.0000
H(36)	0.0449	−0.0521	−1.0826	3.0000
H(37)	−0.0217	0.0686	−1.0942	3.0000

[a] $B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos\gamma + 2U_{13}aa^*cc^* \cos\beta + 2U_{23}bb^*cc^* \cos\alpha)$.

can be drawn for the alkoxide moiety of acetals **2a–c**. Acetal **2d** adopts the same configuration at C_5 as **2a–c** although its coupling constant $J_{3,5}$ (4 Hz) has a higher

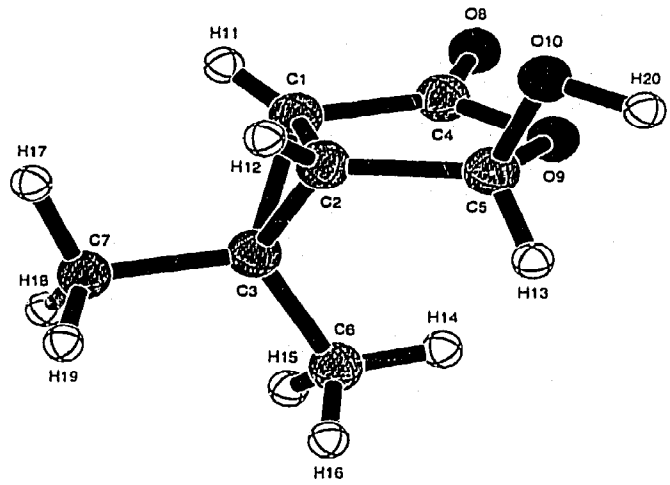
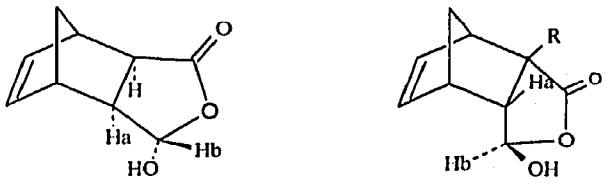


Fig 1. Molecular structure and atom numbering scheme for biocartol **A**.

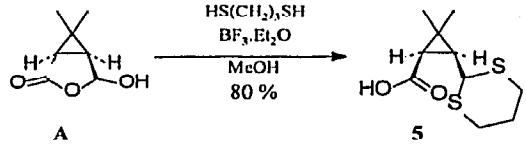
value (scheme 4). The presence of a *trans* diastereoisomer is generally observed with cyclic compounds such as lactols. Thus, on the basis of a $J_{a,b}$ value of 1.5–3 Hz, Canonne et al [10] have shown that several bicyclic formylcarboxylic acids are *trans* diastereoisomers:



Scheme 5

DCC/DMAP-catalyzed esterification using dithiane protection

In order to overcome the shortcomings of the two above procedures, we have explored the feasibility of a rational, more efficient synthesis. The reactivity of biocartol versus hydroxylic functions was improved by keeping it in the open form by formyl group protection (scheme 6). Thus, propane-1,3-dithiol was reacted with biocartol in the presence of boron trifluoride etherate to give the desired dithian-2-yl-substituted carboxylic acid **5**.



Scheme 6

The reaction of **5** with alcohols and phenols catalyzed by DCC-DMAP proceeded with complete reten-

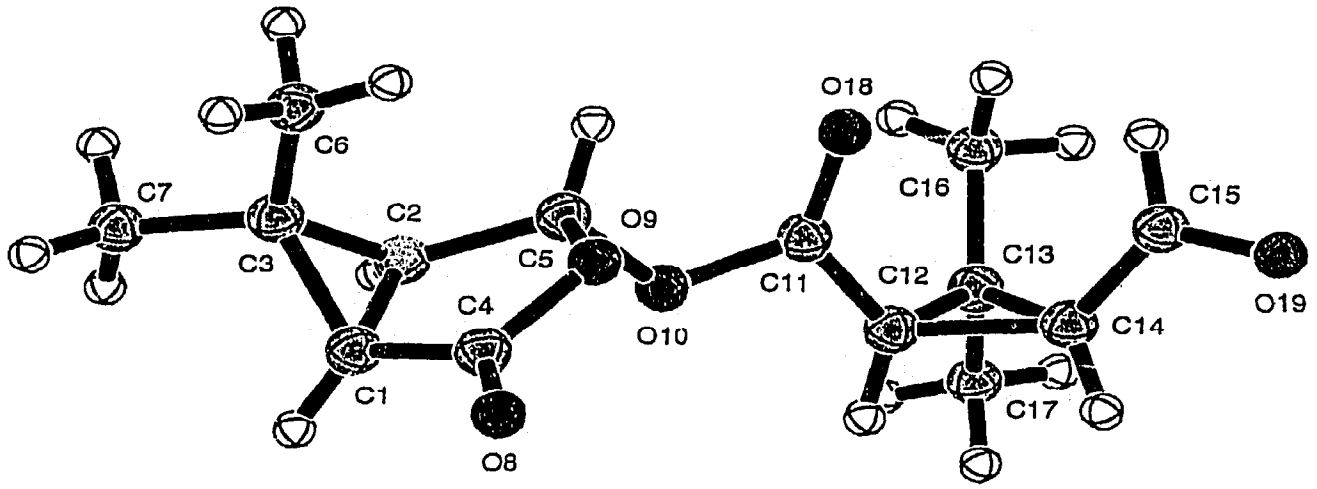
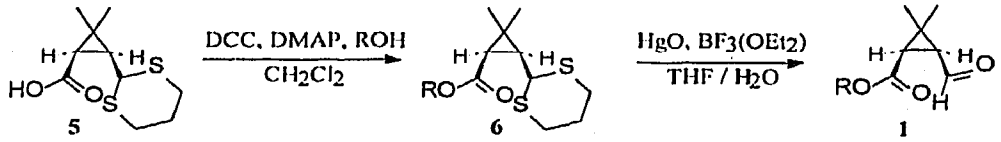


Fig 2. Molecular structure and atom numbering scheme for biocartol 'dimer' **3**.

Table VIII. Yields of protected esters **6a–g** and aldehydo esters **1a–g**.

R	*Compounds* **6**	*Yield*[a] *(%)*	*Compounds* **1**	*Yield*[b] *(%)*	*Overall yield*[c] *(%)*
Me	a	87	a	85	59
Np	d	94	d	90	68
p-NO_2–C_6H_4	e	93	e	95	70
m-NO_2–C_6H_4	f	77	f	85	52
Bornyl	g	85	g	91	62

[a] After column chromatography; [b] after crystallisation for **1e** and **1f**; [c] overall yield of the reaction sequence **A** → **5** → **6** → **1**.



Scheme 7

tion of configuration to esters **6a,d–g** in good yields (table VIII). Finally, the classic deprotection [11] of the dithiane function of **6a,d–g** gave the desired aldehydo esters **1a,d–g** (scheme 7). Proton and carbon NMR resonance assignments of compounds **5**, **6d–g** are presented in tables IX and X.

Conclusion

The three-step method described above allows a facile and flexible preparation of biocartol esters. Phenols and hindered primary or secondary alcohols lead to the corresponding esters in overall satisfactory yield and excellent stereochemical purity. This method has now been extended to the preparation of biocartol amides [12].

Experimental section

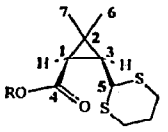
Materials

Reagent-grade reactants and solvents were used as received from chemical suppliers.

Measurements

^1H and ^{13}C NMR spectra were obtained at ambient temperature on Bruker AC 200, AM 300 or AM 400 spectrometers using deuterated chloroform solutions with $CHCl_3$ (δ = 7.24 ppm) and $CDCl_3$ (δ = 76.9 ppm) as internal standards respectively. Spectra listed below are tabulated in the following order: chemical shift (δ, ppm), multiplicity (s = singulet, d = doublet, t = triplet, q = quadruplet, m = multiplet, bb = broad band), number of protons, coupling constant (Hz), assignment. Infrared spectra were

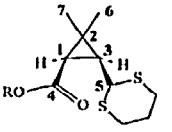
Table IX. ^{1}H NMR data (δ ppm[a]) in $CDCl_3$ of protected acid **5** and esters **6a,d–g**:



Compound	H_1 *(d)*	$J_{1,3}$	H_3 *(dd)*	H_5 *(d)*	$J_{3,5}$	H_6 *or* H_7 *(s)*		*Other protons*
5 (R=H)	1.64	8.6	1.46	4.44	11.4	1.19	1.32	Dithianyl protons: 1.86 (m, 1H); 2.12 (m, 1H); 2.86 (m, 4H)
6a	1.51	8.6	1.25	4.34	11.3	1.04	1.19	R protons: 3.52 (s, OMe, 3H) Dithianyl protons: 1.70 (m, 1H); 1.91 (m, 1H); 2.69 (m, 4H)
6d	1.66	8.7	1.38	4.50	11.5	1.17	1.31	R protons: 3.77 (s, 2H, CH_2); 0.93 (s, 9H, CH_3) Dithianyl protons: 1.84 (m, 1H); 2.05 (m, 1H); 2.82 (m, 4H)
6e	1.90	8.8	1.62	4.36	11.5	1.26	1.39	R protons: 7.28 (d, 2H, J = 9.1 Hz); 8.24 (d, 2H, J = 9.1 Hz) Dithianyl protons: 1.85 (m, 1H); 2.14 (m, 1H); 2.90 (m, 4H)
6f	1.90	8.8	1.68	4.39	11.5	1.23	1.36	R protons: 7.44 (dd, 1H, 8.1 Hz, 2 Hz); 7.50–7.95 (m, 2H, H arom); 8.09 (dd, 1H, 8.1 Hz, 2 Hz) Dithianyl protons: 1.86 (m, 1H); 2.16 (m, 1H); 2.92 (m, 4H)
6g	–	–	–	4.46	10	1.58	1.34	R protons: 0.85 (s, 3H, Me borneol); 0.87 (s, 3H, Me borneol); 0.89 (s, 3H, Me borneol); 1.12 (m, 1H, H borneol); 1.60 (m, 9H, H_3, H_2, dithianyl proton, 6 H borneol); 2.3 (m, 1H, dithianyl proton); 2.9 (m, 4H, dithianyl protons); 4.85 (m, 1H, CH-O-C(O))

At 200 MHz unless specified otherwise; [a] $CHCl_3$ ref: 7.24 ppm.

Table X. ^{13}C NMR data (δ ppm[a]) in $CDCl_3$ of protected acid **5** and esters **6d,e**:



Compound	C_1	C_2	C_3	C_4	C_5	C_6 *or* C_7		*Other carbons*
5	36.9	28.2	29.4	176.1	42.1	13.8	28.8	30.0 (2*CH_2); 25.2 CH_2
6d	36.0	26.8	29.8	170.9	42.3	14.0	28.8	25.6 (2*CH_2); 26.4 (3*CH_3); 30.1 CH_2; 31.2 C; 73.3 CH_2
6e	37.4	28.8	29.4	168.4	42.0	13.6	28.6	30.0 (2*CH_2); 25.4 CH_2 122.6, 125.0, CH arom 145.5, 155.5 C arom

At 50 MHz unless specified otherwise; [a] $CDCl_3$ ref: 76.9 ppm; [b] 75 MHz; [c] 100 MHz.

recorded on a Beckman IR 4250 spectrometer. Mass spectra were measured with a ZAB2-SEQ instrument. Elemental analyses were performed by SCA/CNRS, Vernaison, France.

X-ray crystallography

Crystallographic data for **A** and **3** were obtained using a Siemens P4 diffractometer with graphite-monochromated Cu-Kα and a Syntex diffractometer with graphite-monochromated Mo-Kα radiation, respectively. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 32 carefully centered reflections, corresponded to a primitive orthorhombic cell in both cases. Systematic absences uniquely determined the space group to be $P2_12_12_1$ (#19) for both compounds. The data were collected at a temperature of 25 ± 1 °C using the ω scan technique. The intensities of three representative reflections were measured after every 100 reflections. No decay correction was applied. The linear absorption coefficients for Cu-Kα and Mo-Kα radiation were measured. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied. The structures were solved by direct methods [13] and expanded using Fourier techniques [14]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycles of full-matrix least-squares refinement converged with values of unweighted and weighted agreement factors indicated in table V with other relevant crystallographic information. All calculations were performed for **A** using the Siemens SHELXTL IRIS package, and for **3** using the teXsan [15] crystallographic software package of Molecular Structure Corporation. A list of atomic coordinates and isotropic displacement parameters is shown in table VI for **A** and in table VII for **3**. Additional information such as bond lengths and angles, torsion angles, anisotropic thermal parameters, hydrogen atom positions, and observed and calculated structure factors has been deposited with the British Library Document Supply Centre (see below).

Synthetic procedures

• *Acid-catalyzed esterification.*

General procedure according to Bakshi et al [3]

A stirred solution of 14 mmol biocartol and 2.75 mmol *p*-toluenesulfonic acid in 20 mL methanol or ethanol was refluxed for 7 h. After cooling the mixture at room temperature, 0.4 g sodium acetate was added and the solvent was evaporated. The residue was taken up in petroleum ether and washed twice with water, dried over Na_2SO_4, filtered and evaporated. The slightly yellow oil was then added to 20 mL of a 0.5% aqueous oxalic acid solution. The mixture was then stirred for two hours at room temperature, and then taken up with ethyl acetate and worked up as previously. The resulting slightly yellow liquid was chromatographed on silica gel (90 g), with petroleum ether/ethyl ether mixtures of increasing polarity as eluent and afforded esters **1a,b**. ^{1}H NMR examination indicated that these compounds were contaminated with 1–7% of the epimeric ester **1'a,b**.

• *DCC/DMAP-catalyzed esterification*

■ *(1R,3S)-Benzyl 2,2-dimethyl-3-formylcyclopropane-1-carboxylate* ***1c***

To a stirred solution of 10 g of biocartol (70.4 mmol) and 22.7 g of benzyl alcohol (211 mmol, 3 equiv) in 100 mL CH_2Cl_2 was added dropwise at 10 °C a solution of 0.43 g of DMAP (3.52 mmol, 0.05 equiv) and 16 g of DCC (77.5 mmol, 1.1 equiv) dissolved in 200 mL CH_2Cl_2. The reaction mixture was then stirred for 18 h at room temperature. It was then concentrated and the dicyclohexylurea precipitate was filtered off. The filtrate was washed twice with 10% HCl, and with a saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered, concentrated to half volume, and then 100 mL of cold ether were added. The solid material was filtered off and chromatographed on silica gel with CH_2Cl_2/ethyl acetate (95:5) as eluent, affording the *N*-acylurea **4** and 'dimer' **3** side-products in pure form. The filtrate was evaporated in vacuo, chromatographed on silica gel (200 g) with petroleum ether/ethyl ether (85:15) as eluent and afforded ester **1c** and the corresponding acetal **2c** as colorless oils. After this tedious isolation by column chromatography the indicative proportions of **1c:2c:3:4** were 31:15:36:18. NB: conversion of the starting material **A** is not complete after 18 h reaction time, and formation of dibenzyl ether is observed.

1c: MS (CI/NH_3): m/z 233 (MH^+), 250 (MNH_4^+).

NMR: see tables I and II.

3: R_f = 0.81; eluent (95:5): CH_2Cl_2/AcOEt.

MS (IC/NH_3): m/z 267 (MH^+), 284 (MNH_4^+).

NMR: see tables I and IV.

4: R_f = 0.49; eluent (95:5): CH_2Cl_2/AcOEt.

MS (CI/NH_3): m/z 349 (MH^+).

IR (KBr): 3 250 (NH), 1 695 (C(O)H), 1 648 (C(O)N) cm^{-1}.

NMR: see tables I and II.

The methyl, ethyl and neopentyl esters **1a,b,d** and acetals **2a,b,d** were obtained using the same procedure as described above for **1c**.

1a: MS (CI/NH_3): m/z 157 (MH^+), 174 (MNH_4^+).

IR (neat): 1 745 (CO_2), 1 725 (CO ald) cm^{-1}.

NMR: see tables I and II.

1b: MS (CI/NH_3): m/z 171 (MH^+), 188 (MNH_4^+).

IR: (neat) 1 725 (CO_2), 1 701 (CO ald) cm^{-1}.

NMR: see tables I and II.

1d: MS (FAB$^+$): m/z 213 (MH^+).

NMR: see tables I and II.

2a: MS (CI/NH_3): m/z 157 (MH^+), 174 (MNH_4^+).

NMR: see tables III and IV.

2b–d: NMR: see tables III and IV.

• *DCC/DMAP-catalyzed esterification using dithiane protection*

■ *(1R,3S)-2,2-Dimethyl-3-(1,3-dithian-2-yl)cyclopropane-1-carboxylic acid* ***5***

To a stirred solution of 10 g of biocartol (70.42 mmol) and 10.6 mL of propane-1,3-dithiol (1.5 equiv, d = 1.078) in 450 mL methanol was added dropwise at 0–5 °C 10.4 mL of a solution of $BF_3(OEt_2)$ (1.2 equiv, d = 1.154) in 50 mL methanol. The reaction mixture was further stirred at room temperature for 1 h and 30 min. The solvent was carefully eliminated in vacuo and the residue was taken up in 100 mL of CH_2Cl_2 and washed twice with water. The organic layer was treated with 300 mL of saturated aqueous $NaHCO_3$ solution and stirred vigorously for 15 min. The organic layer was separated after 45 min. To the aqueous layer was added dropwise 75 mL of concentrated HCl (37%, d = 1.186) at 0 °C with vigorous stirring. The white precipitate was filtered off, washed with acidic water (pH 1) and dried. The previous organic layer was extracted again with water and the mixture was kept overnight. HCl treatment of the aqueous layer, similar as above, afforded a second crop of white crystalline acid **5** in pure form. Overall yield 80%.

Mp 127 °C.

Anal calc for $C_{10}H_{16}O_2S_2$: C 51.72, H 6.90, O 13.79, S 27.59. Found: C 51.50, H 6.81, O 13.66, S 27.39.

MS (CI/NH_3): m/z 250 (MNH_4^+), 233 (MH^+).

IR (KBr): 3 222 (OH), 1 724 (CO_2) cm^{-1}.

■ *General procedure for the preparation of protected biocartol esters* ***6a,d–g***

To a stirred and cold (0 °C) solution of 5 g of acid **5** (21.55 mmol) and 2 equiv of alcohol or phenol in 20 mL of CH_2Cl_2 or CH_2Cl_2/DMF dried over alumina was added dropwise during 1 h a solution of DCC (1.1 equiv) and DMAP (0.05 equiv) in 20 mL of CH_2Cl_2. The mixture was stirred for 2–3 h at room temperature. The dicyclohexylurea (DCU) precipitate was filtered off, and the solvent was removed by evaporation. The residue was dissolved in Et_2O (100 mL) and put in the refrigerator overnight. The remaining DCU was filtered off, the solution was washed successively with 0.2 N HCl (4 × 25 mL) and with saturated aqueous $NaHCO_3$ solution (2 × 20 mL), and it was dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by silica gel chromatography with CH_2Cl_2 as eluent to afford the ester **6**. NMR: see tables IX and X.

The methyl, neopentyl, *p*-nitrophenyl, *m*-nitrophenyl and bornyl esters **6a,d–g** were obtained using this procedure, and the yields are reported in table VIII.

6a: NMR: see tables I and II.

6d: MS (FAB$^+$): m/z 132 (MH^+).

NMR: see tables I and II.

6e: Mp 130 °C.

Anal calc for $C_{16}H_{19}O_4NS_2$: C 54.39, H 5.38, O 18.13, N 3.97, S 18.13. Found: C 54.38, H 5.50, O 18.04, N 4.11, S 18.18.

MS (CI/NH_3): 371 (MNH_4^+), 354 (MH^+); (EI) 353 ($M^{+\cdot}$).

IR: (KBr) 1 737 (CO_2) cm^{-1}.

NMR: see tables I and II.

6f: MS (FAB$^+$): 354 (MH^+).

NMR: see tables I and II.

6g: NMR see tables I and II.

■ *General procedure for dithiane deprotection leading to aldehydo esters* **1a,d–g**

To a vigorously stirred solution of 7.4 g of red mercuric oxide (34.0 mmol), 4.2 mL (34.0 mmol) of boron trifluoride etherate solution (d = 1.154) and 15% aqueous tetrahydrofuran (10 mL/g of dithiane) were added dropwise for 15 min 17 mmol of dithiane **1** dissolved in a minimum of tetrahydrofuran. Stirring was maintained for 10–20 min after addition was complete. Diethyl ether was then added, the precipitated inorganic salts were filtered, the ether solution was washed with saturated $NaHCO_3$ solution and brought to neutrality with brine solution. After drying over Na_2SO_4, the ether was evaporated under vacuum to yield aldehydo ester **6**. The methyl, neopentyl, *p*-nitrophenyl, *m*-nitrophenyl and bornyl esters **1a,d–g** were obtained using this procedure, and the yields are reported in table VIII.

1a,d: see above.

1e: Mp = 105 °C.

Anal calc for $C_{13}H_{13}NO_5$: C 59.32, H 4.94, O 30.42, N 5.32. Found: C 59.40, H 5.25, O 30.00, N 5.25.

MS (CI/NH_3): 281 (MNH_4^+), 264 (MH^+); (EI) 264 (MH^+).

IR (KBr): 1 743 (CO_2), 1 696 (CO ald) cm^{-1}.

1f: MS (FAB$^+$): 264 (MH^+).

NMR: see tables I and II.

1g: MS (FAB$^+$): 279 (MH^+).

NMR: see tables I and II.

Supplementary material

Bond lengths and angles, torsion angles, anisotropic displacement parameters, hydrogen atom positions and structure factors have been deposited with the British Library, Document Supply Centre at Boston Spa, Wetherby, West Yorkshire, LS23 7BQ, UK, as supplementary publication No = SUP 90472 and are available on request from the Document Supply Centre.

Acknowledgments

We thank Dr Jean Buendia of Roussel Uclaf for a generous gift of biocartol, Patrick Dubourdeaux and Nathalie Gon for help with the synthesis of the starting materials, Colette Lebrun for mass spectra, and Céline Pérollier for helpful comments.

References

1 a) Martel J, in: *Chirality in Industry*, Collins AN, Sheldrake GN, Crosby J, Eds, Wiley, London, 1992, ch 4
b) Kricf A, Lecomte P, Demoute JP, Dumont W, *Synthesis* (1990) 275
c) Banwell MG, Forman GS, *J Chem Soc, Perkin Trans I* (1996) 2565

2 a) Veyrat M, Maury O, Faverjon F, Over DE, Ramasseul R, Marchon JC, Turowska-Tyrk I, Scheidt WR, *Angew Chem Int Ed Engl* (1994) 33, 220
b) Jentzen W, Simpson MC, Hobbs JD, Song X, Ema T, Nelson NY, Medforth CJ, Smith KM, Veyrat M, Mazzanti M, Ramasseul R, Marchon JC, Takeuchi T, Goddard WA III, Shelnutt JA, *J Am Chem Soc* (1995) 117, 11085
c) Mazzanti M, Veyrat M, Ramasseul R, Marchon JC, Turowska-Tyrk I, Shang M, Scheidt WR, *Inorg Chem* (1996) 35, 3733

3 Bakshi D, Mahidroo VK, Soman R, Dev S, *Tetrahedron* (1989) 45, 767

4 Martel J, Tessier J, Teche A (Roussel Uclaf), Fr Pat 81 18934 (1981)

5 A deuterated chloroform solution (0.5 mL) of biocartol (16.6 mg) exhibits ^1H NMR resonances of both the closed and open forms in a relative ratio **A**/**B** ca 4:1; see tables I and III

6 Enantiopure biocartol was a generous gift of Roussel Uclaf; $[\alpha]_D^{25} = -102$ for a 2% ethanol solution

7 a) Neises B, Steglich W, *Angew Chem Int Ed Engl* (1978) 17, 522
b) Hassner A, Alexanian V, *Tetrahedron Lett* (1978) 4475
c) Mulzer J, in: *Comprehensive Organic Synthesis*, Trost BM, Ed, Pergamon, Oxford, 1991, Vol 6, ch 2.2
d) Ogliaruso MA, Wolfe JF, in: *Synthesis of Carboxylic Acids, Esters and Their Derivatives*, Patai S, Rappoport Z, Eds, Wiley, New York, 1991, p 145 and 378
e) Michelet V, Besnier I, Tanier S, Touzin AM, Genet JP, Demoute JP, *Synthesis* (1995) 165

8 Boden EP, Keck GE, *J Org Chem* (1985) 50, 2394

9 Ortiz de Montellano PR, Dinizo SE, *J Org Chem* (1978) 43, 4323

10 Canonne P, Plamondon J, Akssira M, *Tetrahedron* (1988) 44, 2903

11 Vedejs E, Fuchs PL, *J Org Chem* (1971) 36, 366

12 Pérollier C, Pécaut J, Ramasseul R, Marchon JC, *Bull Soc Chim Fr* (1997) 134, 517

13 Fan Hai-Fu, SAPI91: *Structure Analysis Programs with Intelligent Control*, Rigaku Corporation, Tokyo, Japan, 1991

14 Beurskens PT, Admiraal G, Beurskens G, Bosman WP, Garcia-Granda S, Gould RO, Smits JMM, Smykalla C, DIRDIF92: *The DIRDIF program system, Technical Report of the Crystallography Laboratory*, University of Nijmegen, The Netherlands, 1992

15 teXsan: *Crystal Structure Analysis Package*, Molecular Structure Corporation, 1985 and 1992