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OPTICALLY ACTIVE α-ALKYLSUCCINATES FROM THE STEREOSELECTIVE ALKYLATION OF CHIRAL IMIDE ENOLATES.

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Summary : The chiral oxazolidinones 1 and 2 were alkylated by methyl bromoacetate, then subsequent removal of the chiral auxiliary provided readily with high stereoselectivity the α-alkylated succinates 7 and 8. Acyloin condensation and bromination gave the optically active α-t-butylcyclobutanedione 10.

We have recently reported that optically active dimethyl 2-methylsuccinates, readily available from enzymatic resolution (1), underwent sodium induced acyloin cyclization into (R)(+) or (S)(-) 3-methyl-1,2-disiloxycyclobutenes, which after one pot bromination and base induced $C_4 \longrightarrow C_3$ ring contraction led to 2-methyl-1-hydroxycyclopropanecarboxylic acid derivatives providing useful chiral building blocks (2). It has been effectively shown that the chirality of the stereocenter was retained during all these rearrangements (2). Unfortunately, this enzymatic resolution was only limited to α-methyl and α-benzylsuccinates (1) ; moreover, the alkylation of either diethyl malate (3a) or dimenthyl succinate (3b) for instance, did not allow us to overcome this problem (4). We have found that the best convenient way to α-alkylsuccinates of high enantiomeric excesses was provided by the stereoselective alkylation of chiral carboximide enolates by methyl bromoacetate.

As a matter of fact, following the procedure of D.A. Evans, N-acylation of the oxazolidinones prepared from L-valinol or (1S,2R)-(+) norephedrine led readily to the chiral imides 1 or 2 (5,6), which underwent high stereoselective enolization in THF at -78°C with either lithium or sodium hexamethyldisilylamide to form the corresponding Z-enolates 3 and 4 respectively (5a). After treatment at -78°C with 3 equiv. of methyl bromoacetate (7), the reaction mixture was allowed to warm to -20°C within 1 or 2 h and then quenched at -50°C with 2.5 equiv. of a solution of acetic acid in ether. Filtration and simple chromatography afforded the alkylated products, i.e. the α-succinate derivatives 5 and 6 (8,9) in good or high yields (10) with a diastereoselectivity superior to 95% as shown in Table I. As expected, the alkyl group entered the less shielded face of 3 and 4, i.e. from the side opposite to the bulky substituent of the chiral auxiliary (S, si face or R, Re face : Ik approach) (11).

The simple methanolysis of 5 and 6 (2 equiv. MeONa 1M in MeOH, 0°C) gave the expected methyl α-alkylsuccinates 7 or 8 (8,13) when the substituent R was not too bulky, with good yields and no racemization (entries A, G-I, table II). Otherwise competitive cleavage of the oxazolidinone ring occurred (entries B-F) ; however use of milder basic reagent (LiOOH from LiOH and H_2O_2) (14) allowed to overcome this problem and furthermore to avoid the ready double bond conjugation of the 2-vinylsuccinate 7f (see Table II).

Scheme 1

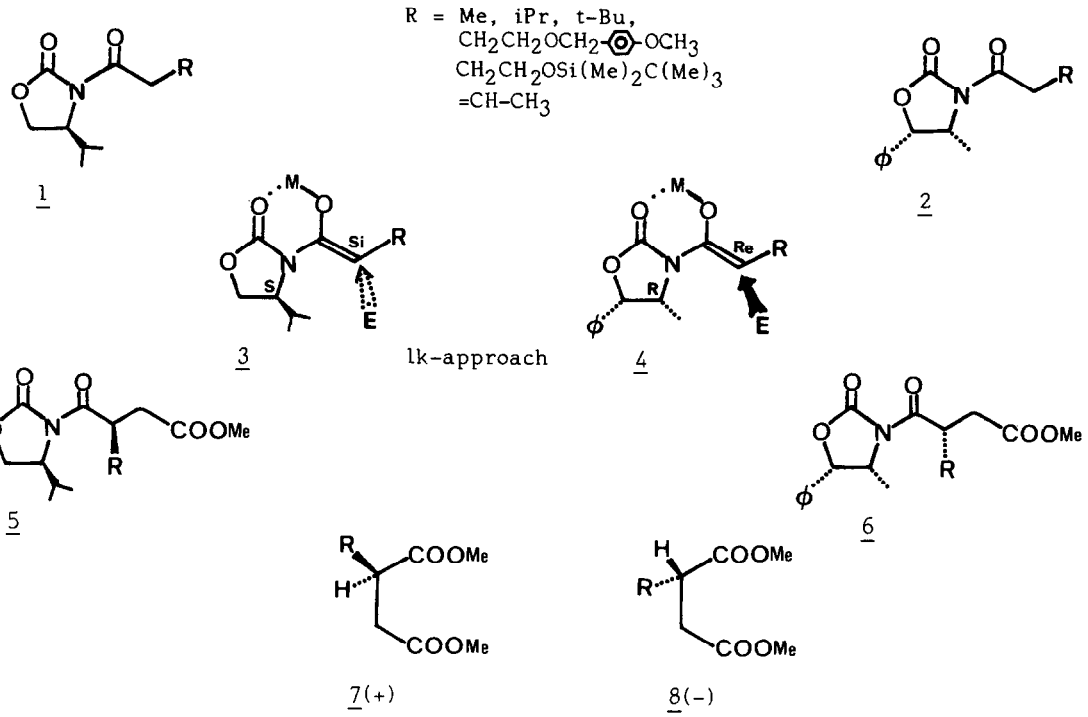


Table I : Alkylation of imides 1 and 2 with methyl bromoacetate (scheme 1)

Entry	R	Imide	Yield (%)	$[\alpha]_D^\circ$	Base	ds%[a]	Conv.	Yield		$[\alpha]_D^\circ CHCl_3$
A	CH_3	1a	93	+95.5	LHMDS	96	94	5a[d]	88	+49
B	iPr	1b	95	+83	NaHMDS	95	87	5b	77	+81
C	tBu	1c	83	+75.5	LHMDS, nBuLi	96	75	5c	72	+88.5
D	tBu	1c			NaHMDS	96	>80	5c	76	+88.5
G	tBu	2c	91	+48.5	LDCA, nBuLi		55	6c	50	+3.3
F	tBu	2c			NaHMDS	98	80	6c	78	+3.3
G	✓OPMB[b]	1d	70	+56	NaHMDS	96	>95	5d	80	+41
H	✓OPMB[b]	2d	82	+29.5	NaHMDS	96	94	6d	84	+7.5
I	✓OSi⊀[b]	1e	64	+55.5	NaHMDS	95	>95	5e	75	+47.5
J	✓CH_3[5f]	1f	95	+105	NaHMDS	90(94)[c]	>98	5g	36(56)	+116

a) ds were determined from ^{1}H-NMR-250 MHz spectra of the crude product ; b) Prepared in direct analogy with reported N-acylation procedure (ref. 6), for silyl ether (entry I) PDC/DMF (12) were required instead of Jones reagent/acetone ; c) Values in parentheses : the base was added over a mixture of imide and $BrCH_2COOMe$ at -78°C (to avoid "self-condensation" of enolates with their precursors) and quenched with AcOH after 1 hr at -78°C ; d) from $BrCH_2COOEt$ alkylation.

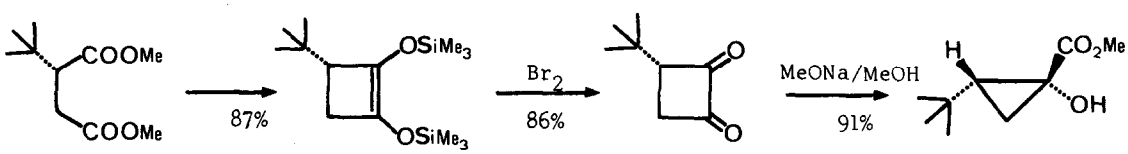
Table II : Transesterification or hydrolysis of alkylated chiral imides

Entry	R	imide	Transesterification or (hydrolysis and CH_2N_2)	time	Prdt	by.p.[a]	Yield	$[\alpha]_D^{\bullet}$ [d]	ee%[b]
A	CH_3	5a	EtONa/EtOH	5 min	7a	<3	84	+4 [e]	96
B	iPr	5b	MeONa/MeOH	3 h	7b[g]	40	55	+17	95
C	tBu	5c	MeONa/MeOH	6-8 h	7c[h]	80	20	+31 [f]	≥99
D	tBu	6c	MeONa/MeOH	2 j	8c[h]	80	20	-30	≥99
E	tBu	6c	LiOOH-Dioxanne (14)	4 j, r.t.	8c	11	70	"	"
F	tBu	6c	LiOOH-THF-H_2O	4 j, -10°	8c	20	55	"	"
G	✓OPMB	5d	MeONa/MeOH	5 min	7d	<1	82	+18	≥99
H	✓OPMB	6d	MeONa/MeOH	20 min	8d	20	69	-18	99
I	✓OSi<	5e	MeONa/MeOH	5 min	7e	11	76	+13	97
J	=CH_2	5f	LiOOH-Dioxanne[c], CH_2N_2	4 h	7f[i]	<1	80	+74.5	95

a) Byproducts were isolated from ring opening of the chiral auxiliary ; b) The ee values were determined by chiral shift reagent Eu(hfc)3 in ^{1}H-NMR high field except for 7a ; c) Methanolysis with MeONa/MeOH entry J gave double bond conjugation ; d) All rotation were recorded in $CHCl_3$ (c=1) except for 7a ; e) Diethyl ester 7a $[\alpha]_D$ = +4.27, c=2.06, CCl_4) (ref. 4) ; f) $[\alpha]_D$ = +14° (c=0.58, ethanol) reported $[\alpha]_D$ = +12.4°, (c=0.58, ethanol) (ref. 15a) ; g) Ref. 16 ; h) Ref. 15 ; i) Ref. 17.

This method allowed the ready preparation, in only three steps, by means of nondestructive and re-usable chiral auxiliaries of a variety of α-substituted succinates such as 7a-f and 8c-d of high optical purity (18). Then acyloin cyclization (Na, $ClSiMe_3$) of succinates 7 or 8 led, in general, to the corresponding 3-alkyl-1,2 disiloxycyclobutenes.

Thus for instance, succinate 8c provided the 3-t-butyldisiloxycyclobutene 9 (8,19), which upon bromination in pentane at -60°C allowed us to obtain the optically active (R)-3-t-butylcyclobutane-1,2-dione 10 (8,20) ($[\alpha]_D$ = -150°, c=0.8, CCl_4), which underwent base induced $C_4 \rightarrow C_3$ ring contraction into the (1R,2R) methyl 1-hydroxy 2-t-butylcyclopropanecarboxylate 11 (8,21), exclusively, as shown by chiral capillary g.c and ^{1}H-NMR in the presence of chiral shift reagent ($Eu(hfc)_3$).



8c 9 10 11

ds 95%

As expected this enantioselective alkylation of chiral imide enolates overcomes the problem of the limitation of the enzymatic resolution of succinates. Synthetic applications of these highly stereoselective chiral blocks are actively in progress and will be reported elsewhere.

References

1) E. Guibé-Jampel, G. Rousseau and J. Salaün, J. Chem. Soc. Chem. Commun., 1987, 1080.
2) J. Salaün and B. Karkour, Tetrahedron Lett., 1987, 28, 4669 ; 1988, 29, 1537.

3) a) G. Fräter, Helv. Chim. Acta, 1979, 62, 2825 and 2829 ; D. Seebach and D. Wasmuth, Helv. Chim. Acta, 1980, 63, 197 ; b) A. Misumi, K. Iwanaga, K. Furuta and H. Yamamoto, J. Am. Chem. Soc., 1985, 107, 3343.

4) B. Karkour, PhD Thesis, Orsay, 1987, France.

5) a) D.A. Evans, J. Bartroli and T.L. Shih, J. Am. Chem. Soc., 1981, 103, 2127 ; b) D.A. Evans, M.D. Ennis and D.J. Mathre, ibid, 1982, 104, 1737 ; c) D.A. Evans, M.D. Ennis and J. Te, ibid, 1984, 106, 1154 ; d) D.A. Evans, M.M. Morrissey and R.L. Dorow, ibid, 1985, 107, 4346 ; e) D.A. Evans, D.J. Mathre and W.L. Scott, J. Org. Chem., 1985, 50, 1830 ; f) D.A. Evans, K.T. Chapman, J. Bisaha, J. Am. Chem. Soc., 1984, 106, 4261 ; g) Ibid, 1988, 110, 1238.

6) 1d-e and 2d were prepared following the procedure in ref. : D.A. Evans and M. Dimare, J. Am. Chem. Soc., 1986, 108, 2476.

7) A. Fadel and J. Salaün, Tetrahedron Lett., 1987, 28, 2243.

8) All new compounds were characterized by 250 MHz ^{1}H and ^{13}C-NMR, IR, MS and when possible by elemental analysis to ± 0.3%.

9) 5b IR (neat) : 1784, 1745, 1700 cm^{-1} ; ^{13}C-NMR (CDCl3) : 175.0 (s), 172.7 (s), 153.6 (s), 62.8 (t), 58.7 (d), 51.5 (q), 44.1 (d), 31.8 (t), 29.6 (d), 27.9 (d), 20.4 (q), 17.9 (q), 17.8 (q), 14.1 (q).
5c IR (CHCl3) : 1785, 1740, 1698 cm^{-1} ; ^{13}C-NMR (CDCl3) : 175.0 (s), 172.8 (s), 154.0 (s), 62.7 (t), 59.1 (d), 51.7 (q), 45.7 (t), 33.3 (t), 33.3 (s), 28.2 (d), 27.3 (q), 18.1 (q), 14.4 (q).
6c : m.p. = 103.7° ; IR (CHCl3) : 1785, 1736, 1700 cm^{-1} ; ^{13}C-NMR (CDCl3) : 175.1 (s), 173.1 (s), 153.1 (s), [6 arom. c : 133.5 (s), 128.7 (3d), 125.7 (2d)], 78.6 (d), 55.4 (d), 51.7 (q), 46.2 (d), 33.3 (t), 33.3 (s), 27.5 (q), 13.5 (q).
5d IR (neat) : 1782, 1740, 1700, 1616,1590 cm^{-1} : ^{13}C-NMR (CDCl3) : 175.3 (s), 172.0 (s), 153.9 (s), [6 arom. C : 159.1 (s), 130.4 (s), 129.2 (2d), 113.6 (2d)], 72.4 (t), 68.0 (t), 62.8 (t), 58.7 (d), 55.2 (q), 51.6 (q), 37.1 (d), 36.7 (t), 32.3 (t), 28.2 (d), 17.8 (q), 14.5 (q).
6d IR (neat) : 1785, 1740, 1700, 1618,1590 cm^{-1} ; ^{13}C-NMR (CDCl3) : 175.4 (s), 172.2 (s), 153.0 (s), [12 arom. C : 159.3 (s), 133.6 (s), 130.6 (s), 129.5 (2d), 128.5 (3d), 125.6 (2d), 113.7 (2d)], 78.4 (d), 72.6 (t), 68.3 (t), 55.1 (q), 54.7 (d), 51.6 (q), 37.3 (d), 36.9 (t), 32.6 (t), 14.1 (q).
5e IR (neat) : 1786, 1745, 1705 cm^{-1} ;^{13}C-NMR (CDCl3) : 175.0 (s), 172.0 (s), 153.5 (s), 62.9 (t), 61.0 (t), 58.6 (d), 51.6 (q), 37.1 (d), 36.0 (t), 34.5 (t), 28.0 (d), 25.8 (q), 18.1 (s), 17.9 (q), 14.3 (q), -5.6 (q).
5f IR (neat) : 1785, 1740, 1700, 1640 cm^{-1} ; ^{13}C-NMR (CDCl3) : 172.7 (s), 171.7 (s), 153.4 (s), 133.9 (d), 118.6 (t), 63.1 (t), 58.8 (d), 51.7 (q), 43.1 (d), 36.0 (t), 28.3 (d), 17.9 (q), 14.5 (q).

10) Lithium diisopropylamide (LDA), lithium diethylamide (LDEA) and lithium dicyclohexylamide (LDCA) which in few cases provided good alkylation, were also tested.

11) D. Seebach and V. Prelog, Angew. Chem. Int. Ed. Engl., 1982, 21, 654.

12) E.J. Corey and G. Schmidt, Tetrahedron Lett., 1979, 399.

13) 7b IR (neat) 1743 cm^{-1} ; ^{13}C-NMR (CDCl3) : 174.8 (s), 172.9 (s), 51.7 (q), 51.7 (q), 51.6 (q), 47.3 (d), 32.8 (t), 30.0 (d), 20.0 (q), 19.5 (q). ^{1}H-NMR as reported (ref. 16).
7c or 8c IR (neat) 1745 cm^{-1}, ^{1}H and ^{13}C-NMR spectra as reported (Ref. 15).
7d or 8d : IR (neat) : 1740, 1616, 1590 cm^{-1} ; ^{1}H-NMR 250 MHz (CDCl3) : 7.25 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.42 (s, CH_2 bzl), 3.81 (s, OCH_3), 3.66 (s, CH_3), 3.65 (s, CH_3), 3.47 (t, J = 6.4 Hz, CH_2O), 3.02 (H-C(2), X part of $ABMX_2$, m), 2.62 (2H-C(3), AB part of $ABM(X_2)$,$\Delta\nu_{AB}$ = 60 Hz, J_{AB} = 17, J = 9.5, 3.5 Hz), 2.97 (m, H-C-C(2)), 2.86 (m, H-C-C(2)), ^{13}C-NMR (CDCl3) : 175.1 (s), 172.2 (s), [6 arom. C : 159.1 (s), 130.2 (s), 129.2 (2d), 113.7 (2d)], 72.6 (t), 67.1 (t), 55.2 (q), 51.7 (q), 38.4 (d), 35.6 (t), 31.6 (t).
7f IR (neat) : 1743, 1645 cm^{-1}, contrary to reported IR data (neat) : 1730, 1610 cm^{-1} (Ref. 17).

14) a) D.A. Evans, E.B. Sjogren, J. Bartroli and R.L. Dow, Tetrahedron Lett. 1986, 27, 4957 ; b) D.A. Evans, T.C. Britton and J.A. Ellman, Tetrahedron Lett., 1987, 28, 6141.

15) a) S. Imajo, H. Kuritani, K. Shingu and M. Nakagawa, J. Org. Chem., 1979, 44, 3587 ; b) D.E. James and J.K. Stille, J. Org. Chem., 1976, 41, 1504 ; c) D.E. James and J.K. Stille, J. Am. Chem. Soc., 1976, 98, 1810.

16) F. Wada and T. Matsuda, Bull. Chem. Soc. Jpn, 1973, 46, 510.

17) J.K. Stille and R. Divakaruni, J. Org. Chem., 1979, 44, 3474.

18) A part of this study was communicated in Organic Chemistry Symposia, on July 1987 at Cambridge (U.K) and on sept. 1987 at Palaiseau (France).

19) 9c : b.p. 35°/0.04 mmHg ; $[\alpha]_D$ = -37.7° (c=1, CCl_4) ; IR (neat) : 1726 cm^{-1} ; ^{1}H-NMR 250 MHz (CDCl3) : 2.27 (H-C(3), X part of ABX, J≈1.25, 4.9 Hz), 1.94 (2H-C(4)), AB part of ABX,$\Delta\nu_{AB}$ = 82 Hz, J_{AB} ≈ 10.5 Hz, J ≈ 1.25, 4.9 Hz), 0.89 (s, 9H, tBu), 0.23 (s, 9H, SiMe3), 0.21 (s, 9H, SiMe3).

20) 10 $[\alpha]_D$ = -150°, (c=0.8, CCl_4) with traces of impurity ; IR (neat) : 1802, 1775 cm^{-1} ; ^{1}H-NMR 250 MHz (CDCl3) : 3.12 (H-C(3), C part of ABC), 3.03 (2H-C(4), AB part of ABC,$\Delta\nu_{AB}$ = 52 Hz, J_{AB} = 23.8 Hz, J ≈ 15.3, 11.3 Hz), 1.05 (s, 9H).

21 11 : $[\alpha]_D$ = +22° (c=0.81, CHCl3) ; IR (CDCl3) : 3500, 3440, 1720 cm^{-1} ; ^{1}H-NMR 250 MHz (CDCl3) : 3.75 (s, CH_3), 2.9 - 2.4 (br, OH), 1.34 (2H-C(3), AB part of ABC, $\Delta\nu_{AB}$ = 20 Hz, J_{AB} = 10.7 Hz, J≈ 7.85, 4.4 Hz), 1.13 (H-C(2), C part of ABC, J ≈ 7.85, 4.4 Hz, q), 1.05 (s, 9H).

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