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STEREOSELECTIVE ADDITIONS TO CARBOXYLIC ACID DIANIONS AND β-LACTONE SUBSTITUTED ESTER ENOLATES

APPLICATION TO THE SYNTHESIS OF RACEMIC EPI-BLASTMYCINONE, δ-MULTISTRIATINE, PARACONIC ESTERS AND LIGNANTYPE DILACTONES

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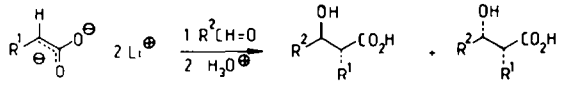
Abstract—New stereoselective syntheses are reported for racemic 4-epi-blastmycinone (**6**) and δ-multistriatine (**13**) utilizing the anti-configurated γ, δ-unsaturated β-hydroxy-carboxylic acids **2a/b**. A diastereo- and enantioselective aldoltype addition of phenylacetic acid dianion to benzaldehyde has been achieved by employing optically active alkoxide amide bases. Finally, highly stereocontrolled additions to the novel β-lactone substituted ester enolates 22 are described.

CC-Connecting additions to chirally substituted enolate systems are the backbone in many stereocontrolled syntheses of acyclic compounds.[1] We report some recent applications of the *anti*[2]-selective reaction of carboxylic acid dianions with aldehydes[3] and some novel stereocontrolled additions to β-lactone derived ester enolates.

Synthesis of racemic 4-epi-blastmycinone and δ-multistriatine. The formation of the β-hydroxycarboxylic acids **2** from carboxylic acid dianions (**1**) and aldehydes proceeds with satisfactory *anti*-selectivity only for bulky substituents R^1 and R^2. For small groups marginal stereocontrol is observed.[3] As we found now, satisfactory amounts of the pure *anti*-diastereomer can be obtained, if lithium diisopropylamide (LDA) prepared by the α-methyl styrene/lithium method[4] is used for the generation of the dianion. Compared to the traditional n-butyllithium procedure a much cleaner reaction occurs and the *anti*-isomer spontaneously crystallizes from the mixture. In this way, we prepared the γ, δ-unsaturated β-hydroxycarboxylic acids **2a** and **2b** in diastereomerically pure form on a multigram scale.



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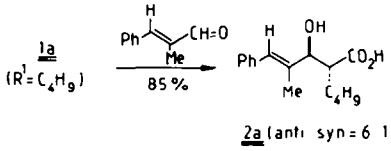
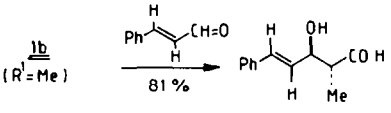
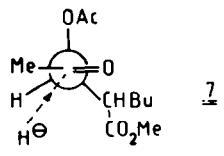


2a (anti : syn = 6 : 1)



2b (anti : syn = 4 : 1)

The double bond in **2a/b** may be considered as an equivalent to a CO-group, so that the overall reaction corresponds to a regio- and stereocontrolled monoaddition of **1a/b** to glyoxal and methyl glyoxal, respectively. This result opens an easy access to racemic 4-*epi*-blastmycinone (**6**) and δ-multistriatine (**13**). Compound **6** has been of some importance in the structural elucidation of the antibiotic antimycin A_3.[5] Compound **13** is a component of the aggregation pheromone of the elm bark beetle *Scolytus multistriatus* and has been prepared by several groups.[6] Our route to **6** and **13** is outlined in Schemes 1 and 2.



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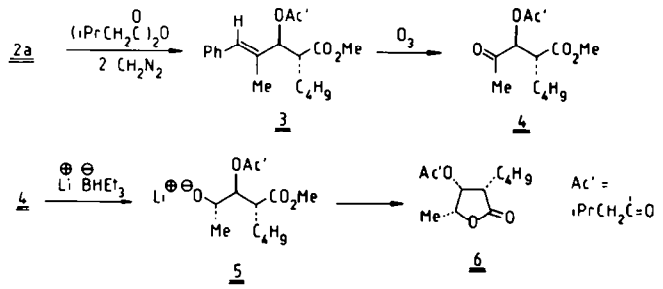
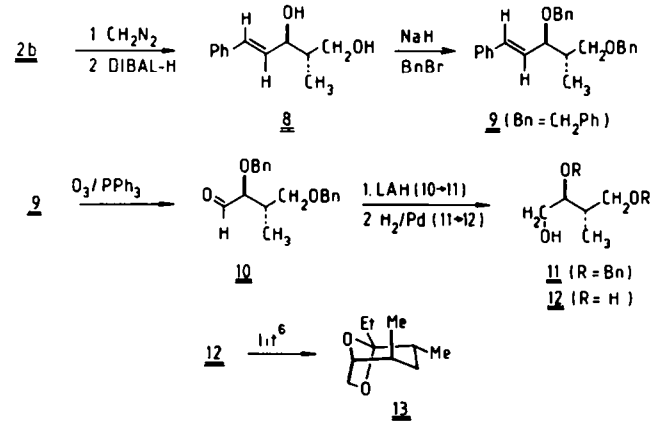


Scheme 1.



Scheme 2.

The reduction step 4→5 with lithium triethylborohydride ("Superhydride") proceeds with 7 : 1-Cram-preference, which may be rationalized in terms of the staggered transition state **7**. The hydride donor attacks the CO-carbon along a Dunitz-trajectory from an *anti*-direction with respect to the O-acyl moiety. To minimize the steric interference with the incoming nucleophile the H- substituent at the chiral center has to be placed next to "H-", which means that the CO-oxygen must adopt the relatively crowded position between the O-acyl function and the remaining C-chain.[7] The alkoxide ester **5** is too instable to be isolated and immediately cyclizes to the final product **6**. The synthesis of **13** was not carried beyond the butane triol **12**, because this intermediate has already been converted into **13** by Mori.[6]

Diastereo- and enantioselective addition of the phenylacetic acid dianion to benzaldehyde

The diastereo- and enantioselective formation of *anti*-configurated *β*-hydroxycarboxylic acids like **2** via an aldoltype addition has been described by Meyers[8] who used a boron substituted chiral oxazoline derivative. We intended to combine the *anti*-selectivity frequently encountered in the additions of **1** to aldehydes[3] with asymmetric induction, however, without attaching the chiral auxiliary covalently to one of the components. Therefore, we generated **1** with the optically active alkoxide amide bases **14** and chose the addition of the phenylacetic acid dianion **1c** to benzaldehyde (**15**) as our model system. Indeed, the *β*-hydroxyacid **2c** was obtained in an optically active form, the best experiment (Table 1, run e) furnishing an ee-value of 85% together with an *anti* : syn-ratio of 6 : 1. Crystallization afforded the diastereomerically pure *anti*-isomer; we made sure by control experiments that this way of isolating the material did not lead to further resolution, and would hence falsify the original ee-value.

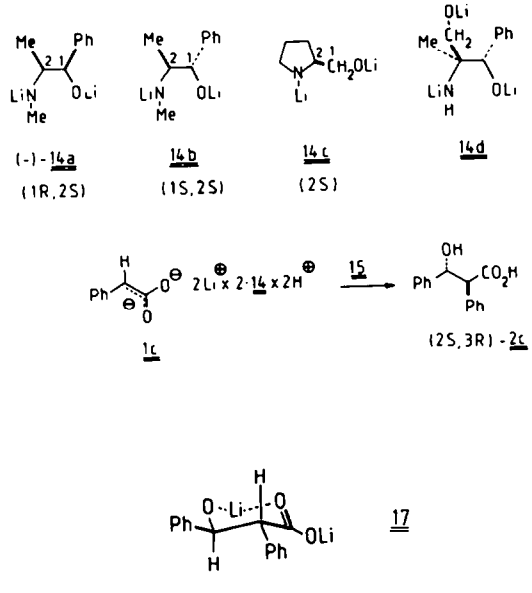


Table 1. Asymmetric Additions of 1c to 15.

Run	Base	2c	Conditions	Yield(%)[a]	$[\alpha]_D^{22}$[b] / % ee
a	(-)-14a	2S,3R	THF/hexane/HMPA 20/5/o.5[c]. -110°C/30 min	85	+68°/58
b	14b	"	as in run a	87	+35 /31
c	14c	"	"	83	+35 /31
d	(+)-14a	2R,3S	"	80	-50 /43[d]
e	14d	2S,3R	"	80	+101 /85
f	(-)-14a +Me_3SiCl	-	"	82	0 /0
g	(-)-15a	2S,3R	THF/hexane/HMPA 20/5/0.5[c]/ 22°C,60min	75	+24 /20
h	"	-	ether/-110°C,30 min	87	0 /0
i	"	2S,3R	THF/hexane 4/1[c],-110°C,30min	80	+48 /42
j	"	"	THF/hexane 4/1[c],-90°C,30min	85	+34 /31
k	"	"	THF/hexane 4/1[c],-70°C,30min	78	+20 /17

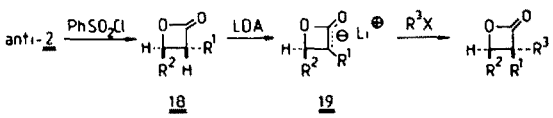
[a]pure anti-acid after crystallization, [b]acetone,c=1 [c]v/v [d]the lower optical yield is due to the lower optical purity of (+)-14a.

The absolute configuration of **2c** is known.[9] To determine the optical yield we first converted racemic **2c** into the methyl ester (**16**) which was then treated with the usual chiral shift reagents and, alternatively, also with Mosher's reagent.[10] In neither case the desired line separation was observed in the 90 MHz ^{1}H-NMR spectrum. Finally, the reaction of **16** with an excess of (+)-camphorsulfonyl chloride in pyridine furnished a mixture of the two diastereomeric sulfonates, which showed base line separated singlets for all four camphor Me groups in the ^{1}H-NMR spectrum. The analytical problem being settled we tried to gain some insight into the induction process (Table 1). The crucial point is the association between **1c** and **14** which is obviously maintained after the proton transfer. (−)-**14a**, **14b** and **14c** which all have (2*S*)-configuration lead to (2*S*, 3*R*)-**2c** (runs a-c), whereas (+)-**14a** (2*R*-configuration) generates the antipode (run d). This indicates that the asymmetric induction originates from the C-2 rather than from the C-1 and **14** and hence, that it is the amido and not the alkoxide function which remains in contact with the carbanionic center in **1c**. The trianionic base **14d** is much more efficient than the dianions **14a-c** (run e). Presumably the additional OLi-anchor enhances the rigidity of the chiral **1/14**-complex. Another experiment (run f) points into the same direction. If (−)-**14a** is first treated with one mole equivalent of Me_3SiCl and then used for the deprotonation racemic **2c** is obtained. In view of the successful deprotonation which is only possible by an NLi- and not by an OLi-moiety it follows that the base has been O-silylated and that a free OLi-function in **14** is indispensable for the induction. Run g demonstrates that the **1/14**-aggregation is maintained even after the aldoltype adduct **17** has been formed. Aldoltype additions of the present kind have been shown to be reversible at 22°.[3] If the system **1c** + (−)-**14a** + **15** is left at this temperature for 1 hr, the resulting **2c** still shows about 30% of its original activity. This means that even after the redissociation of **17** into its components the dianion **1c** retains an asymmetric environment. Finally, from runs h,i,a it may be seen that the induction increases with the solvent polarity and from runs i,j,k that it decreases with rising temperature. High optical rotations have also been obtained for the reaction of **1c** with acetone and benzophenone, but the ee-values could not be determined for those cases. After having finished this study we learnt of similar experiments performed by two other groups[11] who also used optically active amide bases, though not of the alkoxide amide type, for the generation of the enolates and achieved ee's of up to 49% in this way. Surprisingly, much higher inductions have been obtained from chiral amines as additives.[12]

With all due precaution, a speculative mechanistic model is suggested for the **1c/14d**-complex (Fig 1). From the absolute configuration of **2c** it follows that the Si-face[13] of **1c** is attacked by **15** and consequently the Re-face[13] should be shielded. The assumptions of altogether three Li-bridges between the components could explain such a Re-complexation, if one Li is placed between the NH of **14d** and the carbanionic center of **1c**.

Additions to β-lactone substituted ester enolates

Stereocontrolled synthesis of lignantype dilactones and Paraconic ester derivatives. Trans-β-Lactones (**18**) are readily available from **2** and benzenesulfonyl chloride in pyridine.[3] They can be cleanly deprotonated with LDA (prepared by the BuLi method) in THF at −78°. The resulting enolates **19** are stable up to −30° and add a variety of electrophiles from the ring face opposite to R^2 with > 90% (in most cases even > 95%) selectivity.[14]



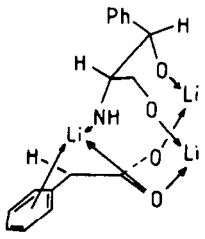
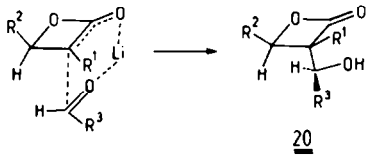


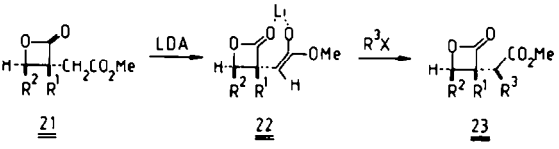
Fig. 1. Speculative model of the **1c/14d**-complex.



20

The addition of aldehydes to **19** proceeds with complete (> 95%) diastereofacial and respectable (> 88%) enantiofacial stereocontrol to give the pseudo-*exo*-isomer **20** selectively.[15] The configuration of racemic **20a** has now been confirmed by X-ray structural determination.

The efficient stereocontrol also of the exocyclic chiral center appears to be due to the rigid planar geometry of the β-lactone ring. We therefore felt that this β-lactone template might also be utilized for controlling the stereochemistry of enolate additions in the sidechain. Specifically, the oxetan-2-on-3-yl-aceticester derivatives **21** were prepared from **19** and methyl bromoacetate and deprotonated (LDA, THF-HMPA, −78°). The resulting ester enolate anion **22** on treatment with a collection of electrophiles furnished the adducts **23** selectively (Table 2), which readily crystallized from the mixture. The structure of **23c** was elucidated by means of X-ray analysis (Fig. 2).



21 **22** **23**

The steric outcome of these additions may be interpreted by postulating a bicyclic roof-life geometry for **22**, by which chelate stabilization is provided to the Li-cation. Electrophiles may be expected to attack **22** from the "convex" face which despite the interfering 3-aryl group seems to be the less shielded one.

A more complicated situation arises if aldehydes are added to **22**. For systems having R^1 = aryl, the reaction may be directed to give the paraconic ester derivatives **24** selectively, by using THF–HMPA (5 : 1) as the solvent. In THF alone, the lignantype

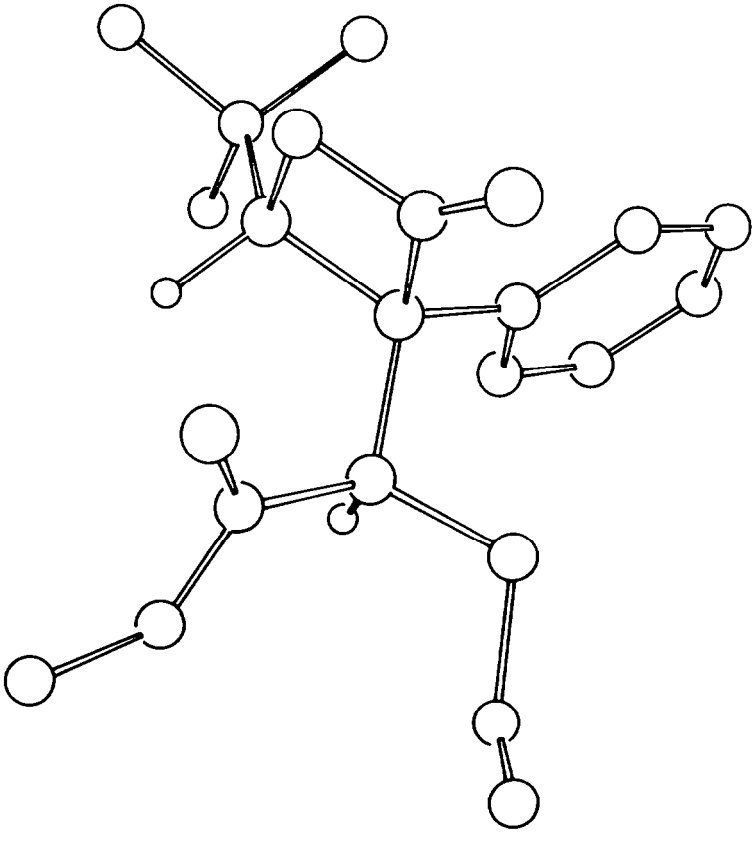


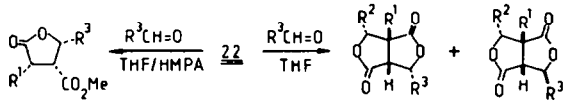
Fig. 2. Crystal structure of (2*R**, 3′*R**, 4′*S**) - Methyl - 2 - (4′ - t - butyl - 3′ - phenyl - 2′ - oxetanon - 3′ - yl) - 4 - pentenoate (**23c**).

Table 2. Stereoselective Alkylations of 22

23	R^1	R^2	R^3-X	Yield(%)	Selectivity [a]	m.p.(°C)
a	Ph	tBu	CH_3-I	91	87:13	68-69
b	"	"	Br-CH_2CO_2Me	81	91:9	151-152
c	"	"	Br-$CH_2CH=CH_2$	85	85:15	67-68
d	"	"	Br-CH_2Ph	93	>98: 2	85-86
e	"	"	Br-$CH_2CH=CHCO_2Me$	80	85:15	103-104
f	Ar[b]	"	CH_3-I	80	>95: 5	104-105
g	"	"	Br-CH_2CO_2Me	89	88:12	134-135
h	"	"	Br-$CH_2CH=CH_2$	91	>95: 5	119-121
i	"	"	Br-CH_2Ph	85	93: 7	158-159
j	Ph	iPr	CH_3-I	74	92: 8	50-51
k	"	"	Br-$CH_2CH=CH_2$	88	>90:10	oil

[a] ^{1}H-NMR-analysis [b] Ar = 3,4-$(OMe)_2C_6H_4$

dilactones[16] **25** are formed with high preference (Table 3). For R^1 = Me only **25** can be obtained.



24 25A 25B

In the case of the mono-lactones **24** only one diastereomer is found. For assigning the relative configuration the inspection of the ^{1}H-NMR spectrum of the di-aryl derivatives **24a/e** is helpful. The ester methyl protons absorb at an unusually highfield position (3.03 and 3.07 ppm in $CDCl_3$), which indicates that the aryl groups and the ester moiety are located on the same ring side. The ester methyl singlets of the mono-aryl derivates **24b-d** appear at 3.40 ppm, which is still about 0.4 ppm upfield from the "normal" position and suggests that at least one of the two substituents R^1 or R^3 must be *cis* to the ester group. Strong evidence that all the mono-lactones **24** do have the same all-*cis*-configuration as assigned to **24a,e** is provided by the coupling constants of the ring protons. These are nearly identical in all cases ($J_{3,4}$ = 7.5 Hz and $J_{4,5}$ = 5.5 Hz), from which it becomes obvious that the geometries cannot be different.

The formation of the dilactones **25** proceeds with much less stereocontrol. Although **25A** is favored in most cases, considerable amounts of **25B** are also found (Table 3.) The two stereoisimers may be readily distinguished by their Hγ,δ-coupling constants

Table 3. Aldehyde Additions to 22

Run	R^1	R^2	R^3	Conditions I[a] Total Yield[c](%) of 24	25	Conditions II[b] Total Yield[c](%) of 24	25	Ratio[d] of 25A : 25B
a	Ph	tBu	Ph	83	10	10	82	60 : 40
b	"	"	iPr	61	12	13	72	85 : 15
c	"	"	tBu	87	<5	<5	71	90 : 10
d	"	"	$nC_{13}H_{27}$	91	<5	<5	87	85 : 15
e	Ar[e]	"	Ph	53	40	<5	82	12 : 88
f	Ph	"	Me	-[f]		<5	85	90 : 10
g	Me	"	Ph	-[g]		<5	82	39 : 61
h	"	"	iPr	-[g]		<5	75	58 : 42

[a] THF-HMPA 5/1 (v/v) , -78°C

[b] THF, -78°C

[c] determined by ^{1}H-NMR (ratios of 24:25) and correlated with the isolated yield of the major isomer

[d] determined by ^{1}H-NMR

[e] Ar = 3,4-$(OMe)_2C_6H_3$ [f] Experiment not performed [g] No addition occurs

which are 2–4.5 Hz for **25B** and 6–9 Hz for **25A**, respectively. These assignments have been made on the basis of Karplus' rule, because the inspection of molecular models reveals dihedral angles for Hγ/Hδ of *ca* 0° (**25A**) and *ca* 100° (**25B**).

A mechanistic rationalization of these findings is presented in Scheme 3. Again, **22** may be safely assumed to be attacked from the "convex" face. Otherwise, the closure of the second lactone ring to form **25** would meet with intolerable ring strain.[17] The primary adduct **26** under the driving force of strain relief opens the β-lactone and closes the γ-lactone to generate **27**, which either cyclizes to **25** or undergoes a retro-aldolization cleavage leading to the new enolate **28**. The second pathway predominates if the Li-chelate in **27** which catalyzes the formation of **25** is weakened by the HMPA-additive. The stereoselective protonation of **28** to **24** is remarkable; presumbly it finds an explanation in the tendency of the two bulky substituents R^3 and R^1 to adopt a pseudoequatorial position at an envelope-shaped γ-lactone ring.

Scheme 3 fails to explain why **24** and **25** are obtained with such different levels of stereocontrol, although they are created via the same intermediates **26/27**. However, it has to be taken into account that in order to get the selective formation of either **24** and **25** different conditions have to be applied. This may well result in different participations of the orientations **A** and **B**, respectively. In those cases where analyzable amounts of both **24** and **25** are formed in one experiment (e.g. Table 3, runs a and e, conditions I) they do in fact belong to the same orientation, namely A.

EXPERIMENTAL

General. ^{1}H-NMR Spectra: Varian A 60, EM 360, EM 390. Tetramethylsilane (TMS) was used as internal standard. IR-Spectra: Perkin–Elmer 125. Optical rotations: Polarimeter LEP 0.005°, Carl Zeiss. M.ps are uncorrected and were determined with a Büchi SMP 20 instrument. All reactions were performed in a flame dried apparatus under an inert atmosphere (Ar of N_2).

Solvents. Tetrahydrofurane (THF) was filtrated over basic alumina, then distilled from lithium aluminiumhydride (LAH). Hexamethyl phosphortriamide (HMPA) was distilled from calcium hydride under reduced pressure. Ether was dried over sodium, then distilled from LAH.

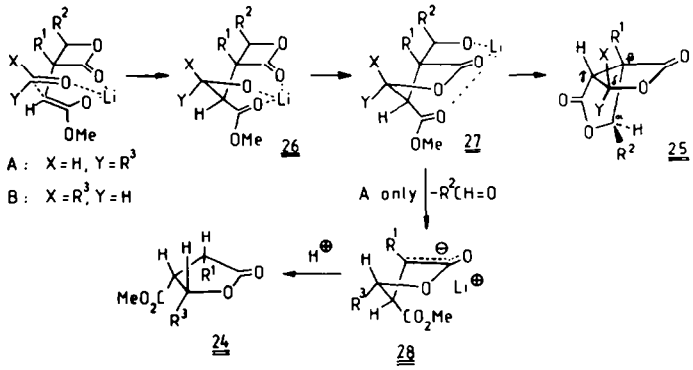
Preparation of lithium diisopropylamide (LDA)[4]

A mixture of 288 ml ether, 48 ml THF, 139 ml (1.00 mole) diisopropylamine and 63 ml α-methyl styrene were contained in a 21 round flask equipped with a mechanical stirrer and a reflux condenser. 6.72 g (1.00 mole) finely cut Li-wire were introduced in small portions; in course of the exothermic reaction the mixture came to a gentle reflux, which was maintained by external heating until all lithium had disappeared and a clear yellow solution of LDA was obtained.

γ, δ-Unsaturated β-hydroxycarboxylic acids **2a/b**

Anti - 2 - Butyl - 3 - hydroxy - 4 - methyl - 5 - phenyl - 4 - pentenoic acid (**2a**). The LDA-soln as obtained above was cooled to −50° and treated dropwise with 57.7 g (0.50 mole) hexanoic acid in 240 ml THF. A colorless ppt of the dianion was formed immediately and the mixture was stirred at room temp for 1 hr to complete the deprotonation. Then the mixture was recooled to −50° and 71.0 g α-methylcinnamaldehyde were introduced from a syringe. After 20 min the cooling was removed and the mixture was hydrolyzed with 100 ml water, extracted with ether, acidified with 2N H_2SO_4 and again extracted with ether. The second organic phase was dried over $MgSO_4$ and evaporated. The ^{1}H-NMR analysis of this crude product indicated an *anti* : *syn*-ratio of 6 : 1. The mixture was dissolved in ether-pentane and kept in the refrigerator for some days. 53.4 g (42%) **2a** crystallized in diastereomerically pure form. 25 g of less pure **2a** were obtained by evaporating the mother liquor. Colorless needles, m.p. 93–94°. ^{1}H-NMR($CDCl_3$): δ = 0.7-1.8 (m, 9H), 1.87 (s, CH_3), 2.7 (mc, 2-H), 4.35 (d, J = 8 Hz, 3-H), 6.52 (s, 5-H), 7.4 (m, 5 Phenyl-H). IR (KBr): 3400, 1700 (C=O), 1490, 1440, 1390, 1285, 1265, 1240, 1190, 1120, 1010, 970, 915, 855, 793, 740 cm^{-1}. (Found: C, 72.99; H, 8.36. Calc. for $C_{16}H_{22}O_3$ (262.24: C, 73.25; H, 8.45%.) In an analogous manner **2b** was prepared from propionic acid cinnamaldehyde in 52% yield of pure **2b**. Description of **2b** see lit.[18]

4-Epi-Blastmycinone (**6**). 12.00 g (0.048 mole) **2a** were treated with 8.94 g (0.048 mole) isovaleric anhydride in 50 ml pyridine. After 4 days at 22° the solvent was removed under reduced pressure and the oily residue was hydrolyzed with 2N H_2SO_4, extracted with ether, dried and evaporated. The crude O-acylated acid was then treated with an ethereal soln of diazomethane until no more N_2 was evolved. Then the ether was evaporated and the product was distilled at 0.001 mm. 13.50 g (72%) *anti* - Methyl - 2 - butyl - 3 - isovaleroxy - 4 - methyl - 5 - phenyl - (E) - 4 - pentenoate (**3**) were obtained with b.p. 150–160°/0.001 mm as a slightly yellow oil. ^{1}H-NMR($CDCl_3$): δ = 0.7–1.8 (m, 16H), 1.85 (s, CH_3), 2.14 (m, 2H), 2.80 (mc, 2-H), 3.68 (s, OCH_3), 5.47 (d, J = 10 Hz, 3-H), 6.65 (s, 5-H), 7.3 (m, 5 phenyl-H). IR (neat): 3069, 3040, 1740 (C=O), 1487, 1160, 980, 915, 735, 720 cm^{-1}. (Found: C, 73.54; H, 8.70. Calc. for $C_{22}H_{32}O_4$



Scheme 3.

(360.49: C, 73.30; H, 8.95%.) 13.40 g (0.037 mole) **3** were treated with O_3 in 200 ml CH_2Cl_2 at $-78°$ until a blue soln was obtained. Then 9.69 g (0.37 mole) triphenyl phosphine were added and the mixture was allowed to stand overnight. Then the solvent was evaporated and the residue was distilled to give 9.12 g (85%) of *anti*-**4** as a colorless oil of b.p. 130–140° 0.001 mm. ^{1}H-NMR($CDCl_3$): δ = 0.9–2.0 (m, 16H), 2.16 (s, CH_3), 2.25 (m, 2H), 3.05 (m, 2-H), 3.65 (s, OCH_3), 5.18 (d, J = 5 Hz, 3-H). IR (neat): 2960, 2930, 1740 (C=O), 1465, 1430, 1355, 1287, 1160, 1115, 1000 cm^{-1} (Found C, 63.39; H, 9.22. Calc for $C_{15}H_{26}O_5$ (286.17) C, 62.91; H, 9.15%.) 8.85 g (0.030 mole) **4** were dissolved in 200 ml THF and treated dropwise at 0° with 30 ml $LiBEt_3H$ (1M in THF). After 4 hr at 0° 2N H_2SO_4 was added and the mixture was extracted with ether. The organic layer was washed with water until neutral, dried and evaporated. After distillation 6.00 g (68%) **6** were obtained which were contaminated with 12% (^{1}H-NMR analysis) of the 5-epimer. Column chromatography (silicagel, pentane–ether 1 : 1) cleanly separated these two isomers whose spectral data were in full accord with those reported in lit.[5]

δ-Multistriatine (**13**). 20.6 g (0.100 mole) **2b** were methylated with diazomethane. The crude ester was dissolved in 200 ml ether and treated with 330 ml DIBAL-H (1M in hexane) at $-20°$ for 3 hr and then hydrolyzed with 2N H_2SO_4. After usual workup the crude product was purified by column chromatography (siliciagel, ether–pentane 3 : 1) to give 13.50 g (65%) of crystalline *anti*-**8**. Colorless needles, m.p. 82–83° (ether). ^{1}H-NMR($CDCl_3$): δ = 0.90 (d, J = 7 Hz, CH_3), 2.0 (mc, 2-H, 3.33 (s, 2OH), 3.73 (mc, CH_2O), 4.17 (t, J = 7 Hz, 3-H), 6.05 (dd, J = 7 and 18 Hz, 4-H), 6.60 (d, J = 18 Hz, 5-H), 7.2 (m, 5 phenyl-H). IR (KBr): 3300 (OH), 2980, 2990, 2880, 1465, 1455, 1265, 1130, 1050, 980, 965, 745, 685 cm^{-1}. (Found: C, 74.80; H, 8.32. Calc. for $C_{12}H_{16}O_2$ (192.13): C, 74.97; H, 8.39%.) 9.60 g (0.050 mole) **8** were added to a mixture of 2.50 g NaH, 50 ml THF and 80 ml DMSO which had been heated to 80° for 45 min before. After additional 50 min at 80° 11 ml benzyl bromide were added and the resulting mixture was stirred at 50° for 30 min. Then it was poured into water and worked up in the usual manner. The crude product was purified by column chromatography (silicagel, ether–pentane 1 : 3) to give 14.60 g (85%) of **9**. ^{1}H-NMR($CDCl_3$): δ = 1.00 (d, J = 7 Hz, CH_3), 2.13 (mc, 2-H), 3.50 (d, J = 6 Hz, CH_2O), 3.99 (t, J = 6 Hz, 3-H), benzyl-CH_2 at 4.33 and 4.60 (AB-spectrum) with J = 12 Hz, 6.01 (dd, J = 6 and 17 Hz, 4-H), 6.53 (d, J = 17 Hz, 5-H), 7.2 (m, 5 phenyl-H).

12.80 g of this ether were ozonized as described above to furnish 8.64 g (84%) of *anti*-**10** which was purified by column chromatography (silicagel, pentane-ether 7 : 1). ^{1}H-NMR($CDCl_3$): δ = 0.97 (d, J = 7 Hz, CH_3), 2.05–2.7 (m, 3-H), 3.1–3.8 (m, 2- and 4-H), 4.40 (s, benzyl-CH_2), second benzyl CH_2 AB-system at 4.43, 4.67, J = 12 Hz, 7.25 (s, 5 Phenyl-H), 7.30 (s, 5 Phenyl-H), 9.70 (d, J = 2 Hz, CH=O). IR (neat): 2980, 2960, 2860, 1730 (C=O), 1456, 1192, 1030, 738, 698 cm.$^{-1}$ (Found: C, 76.48; H, 7.45. Calc for $C_{19}H_{22}O_3$ (298.40): C, 76.48; H, 7.43%.)

10.00 g (0.034 mole) **10** were reduced with a suspension of 5 g LAH in 150 ml THF at 22° for 30 min. After the usual hydrolytic workup 9.00 g (89%) of *anti*-**11** were isolated ^{1}H-NMR($CDCl_3$): δ = 0.97 (d, J = 7 Hz, CH_3), 1.8–2.3 (m, 3-H), 2.50 (OH), 3.3–3.8 (m, 5H) 4.4–4.65 (m, benzyl-CH_2), 7.3 (m, 10 phenyl-H). IR (neat): 3440, 2875, 1445, 1090, 1066, 1028, 734, 692 cm^{-1}. (Found: C, 75.62; H, 7.90. Calc. for $C_{19}H_{24}O_3$ (300.4): C, 75.97; H, 8.05%.) 8.00 g (0.026 mole) 11 were hydrogenated in 200 ml MeOH and 1 ml conc HCl over 1.0 g 10% Pd-C at 1 atm/22° to give 3.20 g (100%) *anti*-**12** which was converted into the 1,2-acetonide according to lit.[6] Both **12** and its acetonide were identical in all respects with the materials described in lit.[6]

Asymmetric addition of **1c** *to* **15**. 0.010 mole of the corresponding amino alcohol were treated with 13 ml (**14a-c**) and 20 ml (**14d**) of n-BuLi (1.6 M in hexane) 50 ml THF at $-78°$ for 30 min. Then 0.680 g (0.0050 mole) phenylacetic acid in 30 ml THF were added and the mixture was stirred at 22° for 30 min. Then 2 ml HMPA were added and after cooling to $-110°$ 2 ml **15** were introduced from a syringe. After 15 min at -100 the mixture was worked up as usual and afforded an oily mixture of *anti*- and *syn*-**2c**, from which 980 mg (80%) of (2*R*, 3*S*)-**2c** of m.p. 180–181° were isolated by crystallization from chloroform. Modifications of this procedure and data see Table 1.

Deprotonation and alkylation of methyl - (c - 4 - alkyl - r - 3 - phenyl - 2 - oxetanon - 3 - yl) - acetates (**21**)

Compounds **21a-d** were prepared from the corresponding β-lactones according to lit.[14] 0.0090 mole **20a-d** were dissolved in 10 ml THF + 8 ml HMPA and slowly added to a mixture of 1.5 ml diisopropylamine and 6.5 ml n-BuLi (1.5 M in hexane) in 125 ml THF at $-78°$. After 30 min 2 mole equiv of the electrophiles listed in Table 2 were introduced via a syringe and the mixture was then stirred at $-78°$ for 16–20 hr. The usual workup furnished oily material, which was analyzed by ^{1}H-NMR. Then the crude product was crystallized from ether-pentane at 6°. As an example, some data are given for (2*R**, 3′*R**, 4′*S**)-**23d**. Colorless crystals, m.p. 85–86°. ^{1}H-NMR($CDCl_3$): δ = 0.73 (S, tBu), ABX-system of the sidechain-H: δ_A = 2.53, δ_B = 3.08, δ_X = 3.45, J_{AB} = 12.5 Hz, J_{AX} = 3.0 Hz, J_{BX} = 11.0 Hz; 3.55 (s, OCH_3), 4.28 (S, CH-tBu), 6.88–7.40 (m, 10 phenyl-H). IR (KBr): 3060, 3022, 2958, 1819 (C=O), 1739 (C=O), 1360, 1160, 1122, 879, 748, 698 cm^{-1} (Found: C, 75.40; H, 7.17. Calc for $C_{23}H_{26}O_4$ (366.44): C, 75.38; H, 7.15%.)

Additions of aldehydes to **22**

Synthesis of paraconic esters **24** *and lingnantype dilactones* **25**. The ester enolates **22** were prepared as described above from 0.0010 mole **21**. Then conditions I and II were applied. *Conditions I.* 50 ml HMPA were added to the soln of the enolate and after additional 10 min 3 mole equivs of the aldehyde were introduced via syringe. The mixture was then stirred for 30 min and then quenched with 2N H_2SO_4. The product was isolated by the usual workup procedure and crystallization for ether–pentane. Yields and m.p. see Table 3. As a particular example some data are given for **24a**.

Methyl - (c - 5 - phenyl - 3 - c - phenyl - 2 - oxolan - 4 - carboxylate) (**24a**). m.p. 157–158° ($CHCl_3$). ^{1}H-NMR(d_6-acetone): δ = 3.03 (s, OCH_3), 4.22 (dd, J = 5.5 and 7.5 Hz, 4-H), 4.73 (d, J = 7.5 Hz, 3-H), 5.95 (d, J = 5.5 Hz, 5-H), 7.3 (m, 10 phenyl-H). IR (KBr): 3085, 3060, 3030, 2950, 1962 (C=O), 1733 (C=O), 1200, 1164, 747, 696 cm^{-1}. (Found: C, 72.78; H, 5.51. Calc. for $C_{18}H_{16}O_4$ (296.31): C, 72.96; H 5.44%.)

Conditions II. 3 Mole equivs of the aldehyde were added to **22** immediately. The yellow mixture was stirred at $-78°$ for 40 min and then worked up as usual. The crude product was analyzed by ^{1}H-NMR and then crystallized from ether-pentane. Yields and ratios of **25A:25B** see Table 3. As particular examples (1*R**, 4*R**, 5*S**, 8*S**) and (1*R**, 4*S**, 5*S**, 8*S**)-**25Aa** and **25B** are described.

Compound **25Aa**: m.p. 188–189°. ^{1}H-NMR($CDCl_3$): δ = 1.05 (s, tBu), 3.76 (d, J = 7.2 Hz, γ-H), 4.52 (s, α-H), 5.44 (d, J = 7.2 Hz, δ-H), 7.30, 7.41 (s, 10 phenyl-H). IR (KBr): 2960, 2920, 1785, 1765 (C=O), 1290, 1280, 1190, 1180, 740, 695 cm^{-1}. (Found: C, 75.52, H, 6.33. Calc for $C_{22}H_{22}O_4$ (350.40): C, 75.41; H, 6.33%.)

Compound **25Ba**: m.p. 163–164: ^{1}H-NMR($CDCl_3$): δ = 1.08 (s, tBu), 3.83 (d, J = 2.8 Hz, γ-H), 4.60 (s, α-H), 5.78 (d, J = 2.8 Hz, δ-H), 7.0–7.5 (m, 10 phenyl-H. IR (KBr): 3060, 2960, 1173 (C=O) 1241, 1223, 1174, 1151, 760, 747, 695 cm^{-1}. (Found: C, 75.61; H, 6.41%.)

X-Ray structural determinations of **20a** and **23c**

Intensity data were recorded on a Nicolet P3 diffractometer. The structures were solved by direct methods

using the SHELXTL program system and defined by least squares.

Compound **20a**: Crystal data: $C_{15}H_{20}O_3$ (248.31), m.p. 144–145° orthorhombic space group $P2_12_12_1$, A = 6.404 (5), b = 14.22 (1), c = 14.96 (2) Å. 1362 Å,^{3} $Z = 4$, $D_c = 1.21\ g\,cm^{-3}$, $F(000) = 536$, μ (Mo-Kα) = $0.9\ cm^{-1}$. Intensity data were recorded at −35° graphite-monochromated. Mo-Kα-X-radiation, $\lambda = 0.71069$ Å), ω-scan with $2.0 < \dot{\omega} < 29.3°\ min^{-1}$ and $2 < 2\Theta < 42°$. A total of 886 reflections were collected, from which 782 reflections having $I > 2\sigma$ were used to solve and refine the structure. The final refinement converged to $R_1 = 0.0578$ and $R_2 = 0.0591$.

Compound **23c**: Crystal data: $C_{19}H_{24}O_4$, M = 316.38, m.p. 67–68°, monoclinic, space group $P2_1/c$, a = 9.059 (6), b = 11.91 (1), c = 18.86 (1) Å. $\beta = 119.14$ (5). U = 1776 Å.^{3} $Z = 4$, $D_c = 1.18\ g\ cm^{-3}$ F (000) = 680, μ (Mo-Kα) = $0.9\ cm^{-1}$. Intensity data were collected at 25°, graphite–monochromated Mo-Kα-X-radiation $\lambda = 0.71069$ Å ω-scan with $1.8 < \dot{\omega} < 29.3°\ min^{-1}$ and $2 < 2\Theta < 42°$. A total of 1904 reflections were collected from which 1371 reflections having $I < 2\sigma$ were used to solve and refine the structure. The final refinement converged to $R_1 = 0.0586$ and $R_2 = 0.0616$.

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