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A GENERAL METHOD FOR THE SYNTHESIS OF 3,4-EPOXY-2-METHYLENEALKANOIC ACID DERIVATIVES USING DIANION OF *N*-PHENYL-2-(PHENYLSULFONYLMETHYL)-PROPENAMIDE

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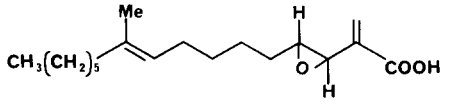
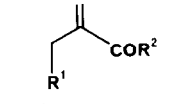
Summary: A general procedure has been developed for the synthesis of 3,4-epoxy-2-methylenealkanoic acid derivatives using dianion of *N*-phenyl-2-(phenylsulfonylmethyl)propenamide and aldehydes.

The α-methylene carbonyl system is a common structural feature of naturally occurring substances possessing cytotoxic, fungitoxic, and growth-inhibitory activity. Although various methods have been reported for the preparation of α-methylene carbonyl compounds, little attention has been given to the synthesis of unusual structural units such as conocandin,[1] isolated from a strain of *Hormococcus conorum*, which has an additional epoxy function at the β,γ-position of the carbonyl group as shown in the structure.[2] In this communication we describe a general method for the preparation of such structural system containing 3,4-epoxy-2-methylene carbonyl functionality.

Our synthetic strategy is based on the utility of dianion 2 because it shows high α-regioselectivity in the reaction with aldehydes (Scheme I). Thus, treatment of the dianion 2 with 1.1 equiv of nonanal in THF containing 2.1 equiv of HMPA at -78°C for 2 h gave, after silica gel-column chromatography, 4-hydroxy-2-methylene-*N*-phenyl-3-(phenylsulfonyl)dodecanamide (3a)[3] in 78% yield. The hydroxy group of 3a was protected as a trimethylsilyl ether, and the resulting ether 4a[4] was treated with 2 equiv of sodium benzeneselenolate in ethanol at 0°C for 2 h, giving exclusively (*E*)-*N*-phenyl-2-phenylselenomethyl-4-trimethylsilyloxy-2-dodecenamide (5a) in 96% yield after extractive isolation and chromatography.[5]

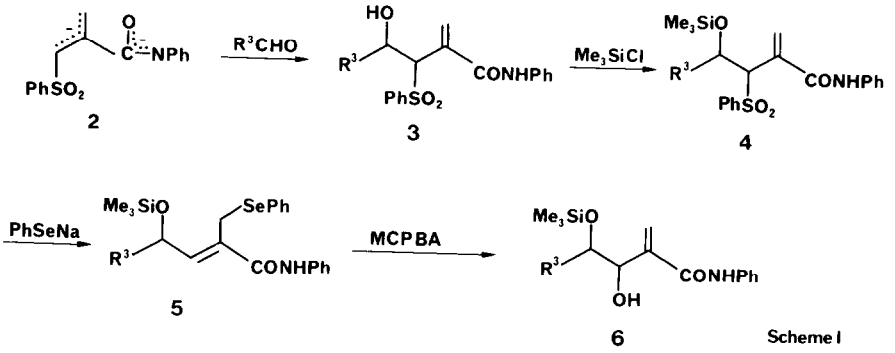


Conocandin



1: R^1=$PhSO_2$; R^2= PhNH

Oxidation of the amide 5a with 1 equiv of MCPBA in dichloromethane at -78°C for 1 h provided 1,2-diol derivative 6a in 88% yield.[6] The results of other examples are summarized in Table 1.

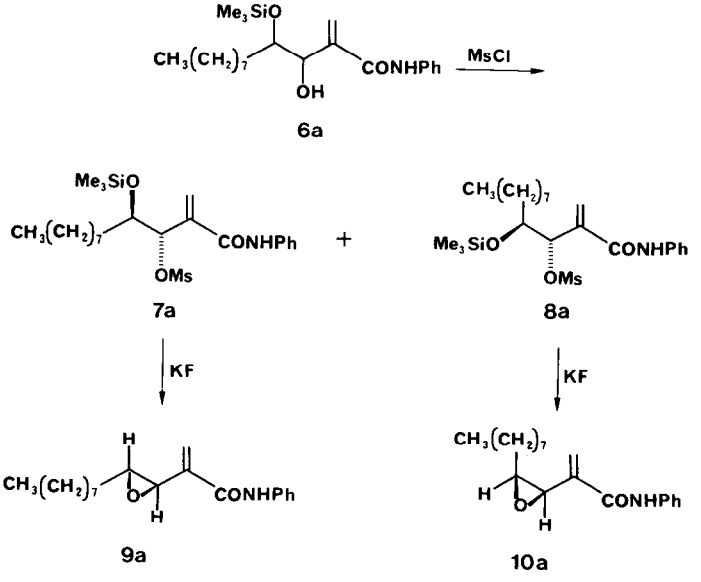


2 3 4 5 6 Scheme I

Reaction of 3-hydroxy-2-methylene-*N*-phenyl-4-(trimethylsilyloxy)dodecanamide (6a) with 1 equiv of methanesulfonyl chloride gave a mixture of stereoisomers 7a (41%) and 8a (27%) which were easily separated by open column chromatography on silica gel using hexane-ethyl acetate (4:1) as eluent.[7]

Table 1. Preparation of Amides 3-6 (See Scheme I)

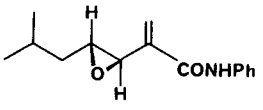
aldehyde	3 (yield)	4 (yield)	5 (yield; *E*/*Z* ratio)	6 (yield)
$n\text{-}C_8H_{17}CHO$	3a (78%)	4a (83%)	5a (96%; 100/0)	6a (88%)
$(CH_3)_2CHCH_2CHO$	3b (56%)	4b (82%)	5b (91%; 94/6)	6b (98%)
$c\text{-}C_6H_{11}CHO$	3c (77%)	4c (76%)	5c (87%; 100/0)	6c (75%)



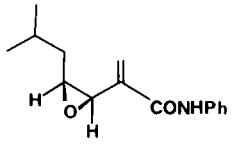
6a 7a 8a 9a 10a

Conversion of trimethylsilyl ethers 7a and 8a into epoxides 9a and 10a was achieved in one step. Thus, reaction of erythro isomer 7a, the more mobile amide, with 2 equiv of potassium fluoride in DMSO afforded exclusively trans-3,4-epoxy-2-methylene-*N*-phenyldodecanamide (9a) in 66% yield.[8] The less mobile amide, threo isomer 8a, upon treatment as described above gave cis-3,4-epoxy-2-methylene-*N*-phenyldodecanamide (10a) in 66% yield.[8] The structural assignments of 9a and 10a were based on the analysis of ^{1}H NMR spectra. The small vicinal coupling constant (J = 2.5 Hz) of 9a confirmed the trans relation of C(3)-H and C(4)-H, while the larger coupling constant (J = 4.5 Hz) of 10a was consistent with the cis stereochemistry.[1,2,9]

Similarly, reaction of 3-hydroxy amide 6b with methanesulfonyl chloride afforded a separable mixture of 7b and 8b in a ratio of about 1:1 which, upon treatment with fluoride ion, furnished the corresponding 3,4-epoxy-2-methylene amides 9b (54%) and 10b (55%), respectively.

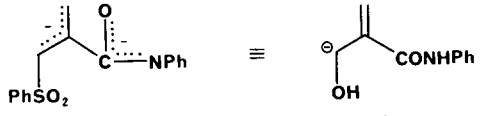


9b



10b

In these synthetic sequences, the dianion 2 is synthetically equivalent to anion 11.



2 11

Since secondary amides can be easily converted to carboxylic acids or esters under very mild conditions,[10] the present method provides a wide variety of 3,4-epoxy-2-methylenealkanoic acid derivatives from the readily available starting materials.

References and Notes

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3. Compound 3a: ^{1}H NMR ($CDCl_3$) δ 8.19 (m, 1H), 7.71-7.89 (m, 2H), 6.89-7.60 (m, 8H), 6.26, 6.13 (s, 1H), 6.07, 5.72 (s, 1H), 4.20-4.72 (m, 2H), 3.40-3.95 (broads, 1H), 0.96-1.72 (m, 14H), 0.60-0.96 (m, 3H); IR (neat) 3320, 1650, 1600, 1310, 1155, 1090 cm^{-1}.
Anal. Calcd for $C_{25}H_{33}NO_4S$: C, 67.69; H, 7.50; N, 3.16. Found: C, 67.48; H, 7.27; N, 3.42.
4. Compound 4a: ^{1}H NMR ($CDCl_3$) δ 8.21 (broads, 1H), 6.82-7.90 (m, 10H), 6.12 (d, J = 5 Hz, 1H), 6.02 (d, J = 5 Hz, 1H), 4.28-4.94 (m, 2H), 0.62-1.94 (m, 17H), 0.15 (s, 9H); IR (neat) 1675, 1605, 1315, 1160, 1100 cm^{-1}. Anal. Calcd for $C_{28}H_{41}NO_4SSi$: C, 65.20; H, 8.01; N, 2.72. Found: C, 65.15; H, 7.86; N, 2.61.
5. Compound 5a: mp 67-68°C. Anal Calcd for $C_{28}H_{41}NO_2SiSe$: C, 63.37; H, 7.79; N; 2.64. Found: C, 63.40; H, 7.64; N, 2.71.
6. Compound 6a: ^{1}H NMR ($CDCl_3$) δ 8.81, 8.59 (broads, 1H), 6.92-7.60 (m, 5H), 5.99 (d, J = 7 Hz, 1H), 5.54 (s, 1H), 4.36 (broads, 1H), 3.26-3.96 (m, 2H), 0.64-1.64 (m, 17H), 0.04 (s, 9H); IR (neat) 3280, 1660, 1600, 1085 cm^{-1}.
Anal. Calcd for $C_{22}H_{37}NO_3Si$: C, 67.47; H, 9.52; N, 3.58. Found: C, 67.17; H, 9.41; N, 3.56.
7. Erythro-isomer 7a: ^{1}H NMR ($CDCl_3$) δ 8.03 (broads, 1H), 6.89-7.45 (m, 5H), 5.92 (s, 1H), 5.63 (s, 1H), 5.22 (d, J = 4 Hz, 1H), 3.89-4.11 (broads, 1H), 2.83 (s, 3H), 0.85-1.75 (m, 14H), 0.51-0.85 (m, 3H), 0.01 (s, 9H); IR (neat) 3310, 1670, 1600, 1360, 1180 cm^{-1}.
Threo-isomer 8a: ^{1}H NMR ($CDCl_3$) δ 7.93 (broads, 1H), 6.88-7.52 (m, 5H), 5.94 (s, 1H), 5.64 (s, 1H), 5.19 (d, J = 5 Hz, 1H), 3.84-4.08 (m, 1H), 2.89 (s, 3H), 0.96-1.65 (m, 14H), 0.63-1.65(m, 3H), 0.01 (s, 9H); IR (neat) 3340, 1670, 1600, 1360, 1185 cm^{-1}.
8. Trans epoxide 9a: ^{1}H NMR ($CDCl_3$) δ 8.68 (broads, 1H), 6.99-7.67 (m, 5H), 6.23 (s, 1H), 5.74 (s, 1H), 3.57 (d, J = 2.5 Hz, 1H), 3.10 (dt, J = 2.5, 5 Hz, 1H), 1.06-2.00 (m, 14H), 0.72-1.06 (m, 3H); IR (neat) 3270, 1660, 1630, 1600, 905, 760 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71, H, 9.03; N, 4.65. Found: C, 75.56; H, 9.05; N, 4.54.
Cis epoxide 10a: ^{1}H NMR ($CDCl_3$) δ 8.32 (broads, 1H), 6.98-7.64 (m, 5H), 6.26 (s, 1H), 5.64 (s, 1H), 3.92 (d, J = 4.5 Hz, 1H), 3.08-3.36 (m, 1H), 0.98-1.78 (m, 14H), 0.64-0.98 (m, 3H); IR (neat) 3280, 1660, 1640, 1600, 770 cm^{-1}.
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