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Direct regio- and stereoselective synthesis of squalene 2,3;22,23-dioxide using dioxiranes

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Abstract—Dimethyldioxirane (**1a**) and its trifluoro analog (**1b**) were employed to achieve selectively the direct transformation of squalene 2,3(*S*)-oxide and of squalene 2,3(*R*)-oxide into the corresponding 2,3(*S*);22(*S*),23-dioxide and 2,3(*R*);22(*R*),23-dioxide, respectively. These transformations were found to occur with convenient regio- and diastereoselectivity, providing easy access to the valuable dioxides metabolites. The powerful methyl(trifluoromethyl)dioxirane (**1b**) is the reagent of choice to achieve optimum yields of the target compounds.

In continuation of our work on selective poly-epoxidations[1] with dimethyldioxirane (DDO) (**1a**)[2a] and methyl(trifluoromethyl)dioxirane (TFDO) (**1b**),[2b,c,3] we undertook to examine the oxidation of a few isoprenoids of choice. Acyclic isoprenoids represent a class of compounds presenting important biological functions that are quite diffused in nature. For instance, the isoprenoid squalene has been demonstrated to be a precursor in the biosynthesis of sterols, a fundamental step in such transformation being the stereospecific cyclization of its squalene 2,3-oxide (**2**), the substrate for cyclase enzymes.[4] Almost all of the initial squalene oxide biosynthesized is converted in cells to lanosterol and then to cholesterol. Under normal metabolic conditions, however, a minor amount of **2** is diverted to another alley forming squalene 2,3(*S*);22(*S*),23-dioxide (**3**);[4] the latter then undergoes transformations analogous to squalene 2,3-oxide, yielding in the end the relatively stable epoxide sterol metabolite 24(*S*),25-epoxycholesterol. When cyclase is inhibited, there is a greater diversion of squalene 2,3-oxide to squalene 2,3;22,23-dioxide.[4b] Thus, a number of efforts have been directed to the synthesis of the key dioxide **3**.[4,5] Such attempts were met with varying degrees of success. Among the valuable entries, particularly elegant is the convergent approach recently reported by Xiong and Corey.[6]

According to this method (sketched in Chart 1), starting with *E*,*E*-farnesyl acetate (**4**), a four step synthetic sequence, which initiates with the enantioselective dihydroxylation of the C(10)=C(11) bond, yields (*S*)-10,11-epoxyfarnesyl bromide (**5**). Then, using Rieke barium[7] coupling of **5** yields the dioxide **3** in ca. 18% yield.

Our own approach began with the initial observation that racemic squalene 2,3-oxide[8] (easily obtained in 22% isolated yield from the reaction of squalene with DDO)[8] regioselectively yielded the corresponding 2,3;22,23-dioxides (racemic) **3a/3b** in ca. 60% overall yield upon reaction of squalene with TFDO under the conditions given in Chart 2. The MS (EI) and ^{1}H–^{13}C NMR analysis of the reaction mixture showed that the diastereomeric 2,3;22,23-dioxides[9] are accompanied mainly by the corresponding regioisomeric 2,3;14,15- and 2,3;18,19-dioxides[8a] in 16% overall yield, plus other products of over oxidation. From this mixture the 2,3;22,23-dioxides could be easily isolated by column chromatography (silica gel, petroleum ether 40–60/Et_2O 3:1).

On this ground, it was decided to explore the stereoselectivities attainable upon reaction of optically active squalene oxides **2a** and **2b** (3*S*-oxido- and 3*R*-oxidosqualene, respectively, Chart 2).

Keywords: Squalene dioxides; Squalene; Epoxidation; Dioxiranes; Dimethyldioxirane; Methyl(trifluoromethyl)dioxirane; Oxidation.
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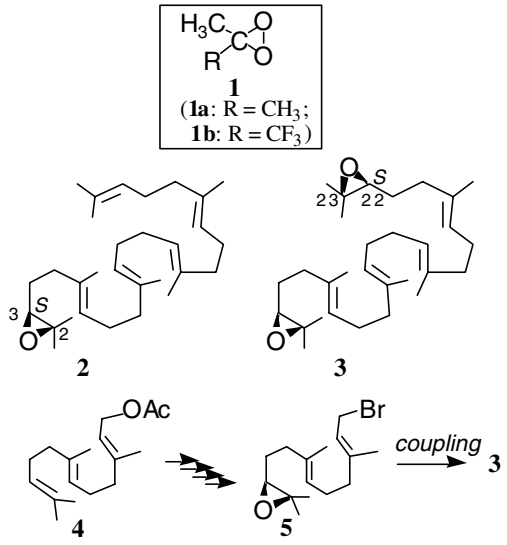

Chart 1.

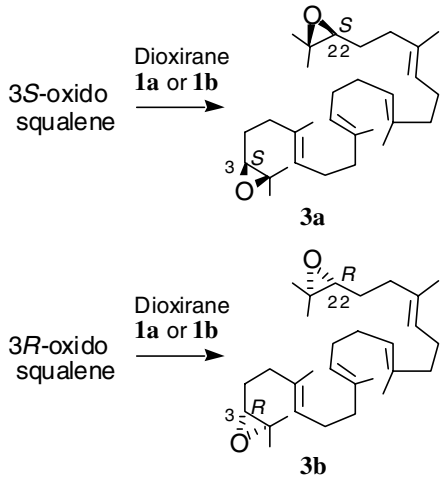

Chart 2.

In fact, it is known[1–3] that reactions performed with dioxiranes **1a**,**b** in isolated form (as solutions in the parent ketones) are best suited to carry out stoichiometric oxidations *under strictly neutral conditions* of acid- or base-sensitive substrates. Dimethyldioxirane (DDO) (**1a**)[2a] and methyl(trifluoromethyl)dioxirane (TFDO)[2c] (**1b**) solutions [0.08–0.1 M in acetone, and 0.7–0.8 M in 1,1,1-trifluoropropanone (TFP), respectively], were prepared as already reported in detail.[2] Squalene 2,3(*S*)-oxide (**2a**),[10a] and squalene 2,3(*R*)-oxide (**2b**),[10b] were synthesized according to the procedure outlined by Corey et al.[7b] starting with optically active (*R*)-2,3-dihydroxy-2,3-dihydrosqualene[11a] or with its (*S*) counterpart,[11b] respectively. The latter materials were made available in high optical purity by the Sharpless enantioselective dihydroxylation of squalene using the commercially available $(DHQD)_2$–PHAL or $(DHQ)_2$–PHAL catalysts.[12]

Dioxirane oxidations of the oxides **2a** and **2b** were routinely carried out by the rapid addition of an aliquot (usually from 0.5 to 3.0 mL, ca. 1.2 equiv) of standardized cold solution of ca. 5 mL of 0.1 M DDO (**1a**) in acetone or 0.7 M TFDO (**1b**) in 1,1,1-trifluoro-2-propanone (TFP) to a stirred solution of the substrate (100–300 mg) in CH_2Cl_2 or acetone (5–30 mL) under the conditions given in Table 1. The reactions were monitored by HPLC and TLC; product isolation simply entailed removal of solvent in vacuo. The diastereomeric 2,3;22,23-dioxides could be separated from the crude mixture, containing also their regioisomers (and higher poly-oxides) as well as starting material, by column chromatography (silica gel, petroleum ether 40–60/Et_2O 3:1).

The optically active 2,3;22,23-dioxides **3a** and **3b** thus isolated gave satisfactory IR, ^1H and ^{13}C NMR spectra. Since the spectroscopic characteristics of the dioxides were not available, we embarked in the synthesis of dioxide *S*,*S*(−)-**3a** by adopting precisely the precursors, reagents, and procedure described by Xiong and Corey.[6] By following this multistep procedure, we were able to obtain squalene 2,3(*S*);22(*S*),23-dioxide (**3a**)[6] as a colorless oil in 5% overall yield ($[\alpha]_D$ −2.2; $CHCl_3$). In fact, we find that the critical final step of this procedure—which involves the mentioned Rieke barium[7] coupling of (*S*)-10,11-epoxyfarnesyl bromide (**5**)—proceeds in ca. 20% yield only. Dioxides **3a** and **3b** obtained by our direct oxidation method presented physical and spectroscopic data in full agreement with the authentic sample made available as above.[13,14]

Data that are representative of the regio- and stereoselectivities attainable in the direct dioxirane oxidation of enantiomeric squalene 2,3-oxides are collected in Table 1. These show that, using the procedure reported herein, both optically active enantiomeric dioxides **3a** and **3b** can be synthesized with high regioselectivity in up to 32% *isolated* yield. For both dioxirane oxidants, the yields in dioxides could be substantially improved on going from solvent methylene chloride to the more polar acetone and on running the reactions at low temperature (−80 °C). It is also worth of notice that each of the dioxides was obtained in high excess with respect to its *meso R*,*S*-distereomer (also formed). In each of the cases examined the optically active squalene 2,3;22,23-dioxides **3a** and **3b** synthesized could be satisfactorily separated from the mixture containing the *meso* form, the starting material, as well as byproducts, employing column chromatography.

One could attempt a rationalization of the stereoselectivities attained on ground of conformational effects involving squalene and squalene oxides in solution. It was first advanced by van Tamelen[15] that the selective high reactivity of squalene terminal C=C bonds, which represents the initial step of the oxidation–cyclization of this key isoprenoid to sterols in vivo, could be ascribed to solvent-induced coiling of the molecule.

Subsequent spectroscopic studies have been addressed to shed light into this phenomenon.[16] In fact, careful ^1H and ^{13}C NMR data, along with molecular mechanics computations, carried out on squalene and on its 2,3-oxide, have pointed to a relatively rigid structure for

Table 1. Stereoselectivity in the oxidation of squalene 2,3-oxide to squalene 2,3;22,23-dioxide using isolated dioxiranes[a]

#	Substrate epoxide[b]	Dioxirane oxidant	*t* (°C)	Solvent	Reaction time (min)	Convn. (%)[c]	Dioxide	Yield (%)[d]	dr[e]
1	*S*(−)-**2a**	DDO (**1a**)	0	CH_2Cl_2	15	72	*S,S*(−)-**3a**	20	82:18
2	*S*(−)-**2a**	DDO (**1a**)	−80	CH_2Cl_2	15	56	*S,S*(−)-**3a**	25	82:18
3	*S*(−)-**2a**	DDO (**1a**)	0	Acetone	15	70	*S,S*(−)-**3a**	20	82:18
4	*S*(−)-**2a**	DDO (**1a**)	−80	Acetone	15	73	*S,S*(−)-**3a**	32	90:10
5	*S*(−)-**2a**	TFDO (**1b**)	0	CH_2Cl_2	3	30	*S,S*(−)-**3a**	15	84:16
6	*S*(−)-**2a**	TFDO (**1b**)	−80	CH_2Cl_2	3	31	*S,S*(−)-**3a**	15	80:20
7	*S*(−)-**2a**	TFDO (**1b**)	0	Acetone	3	22	*S,S*(−)-**3a**	15	83:17
8	*S*(−)-**2a**	TFDO (**1b**)	−80	Acetone	3	40	*S,S*(−)-**3a**	28	85:15
9	*R*(+)-**2b**	DDO (**1a**)	−80	Acetone	15	75	*R,R*(+)-**3b**	30	90:10
10	*R*(+)-**2b**	TFDO (**1b**)	−80	Acetone	3	40	*R,R*(+)-**3b**	22	85:15

[a] All reactions routinely run with initial dioxirane to substrate molar ratio ca. 1.2:1; mixed solvent composition was CH_2Cl_2/TFP ca. 9:1 for oxidations with **1b**, and CH_2Cl_2/acetone ca. 7:3 for oxidations with **1a**.

[b] Percent enantiomeric excess (% ee) of 1,2-oxides starting materials were 92% for **2a** and 75% for its enantiomer **2b**; % ee were estimated (±2%) upon comparison of optical rotations with the literature values (Ref. 7b).

[c] As determined by HPLC (Hewlett–Packard mod. 1050, UV detector) of the reaction mixture, employing a chiral stationary phase (DAICEL Chiralcel OD, 25 cm × 0.46 cm ID; 5% *i*-PrOH/95% *n*-hexane, 1.5 mL/min).

[d] Isolated yield, as determined (±5%) based on the amount of starting material converted. Percent optical yields practically unchanged with respect to those of starting materials, that is, 90% for *S,S*(−)-**3a** ($[\alpha]_D$ −2.0, *c* 1.3, $CHCl_3$) and 73% for *R,R*(+)-**3b** ($[\alpha]_D$ +1.8, *c* 1.6, $CHCl_3$). The optical yields were estimated upon comparison with an authentic sample of the *S,S*(−)-dioxide (**3a**) ($[\alpha]_D$ −2.2, *c* 1.8, $CHCl_3$; 92% o.p.) synthesized according to the multistep method in Ref. 6.

[e] Diastereomeric ratio of the prevalent diastereomer over its minor counterpart, as determined by HPLC employing the same chiral stationary phase column reported in footnote c.

the central part of the chain, with staggered conformations along the C11–C12 bond being favored. Similar to squalene, the chain of squalene 2,3-oxide in solution would undergo conformational equilibria involving the mobile tails moving around a more rigid central portion. This gives the squalene chain the form of a dynamic 'precoil', for instance as shown in Figure 1. The mobile chain ends would sweep the surrounding space and are ready to react; however, at the same time they would shield the central part of the molecule, which becomes somewhat protected from electrophilic attack by the oxidant.[16]

On the other hand, the diastereoselectivity observed—that is, the observed prevalence of the *S,S*-dioxide **3a** or *R,R*-dioxide **3b**, respectively, over their *meso* counterpart—is more difficult to unravel. To envisage π-facial selectivity from a simple standpoint, one might of course invoke the notorious sensitivity of dioxirane oxidations to steric effects and explain the stereoselectivity on grounds of squalene 2,3-oxide preferred conformations akin to that represented in Figure 1. The mechanistic details being as it may, the feat of the *direct* regioselective transformation of the 2,3-oxide into the 2,3;22,23-dioxide is notable.

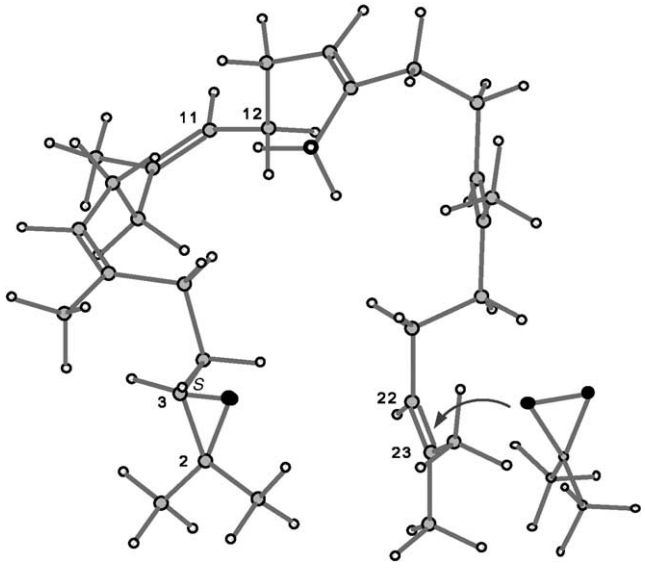

Figure 1. Stereoselectivity of dimethyldioxirane attack at a precoiled squalene 2,3(*S*)-oxide conformation (MM2).

The more than adequate yields attained compare favorably with those attainable with the available multistep methods.[6,7] Adopting the dioxirane oxidation described herein, not only the *S,S*-dioxide metabolite can be obtained, but also its precious *R,R*-enantiomer was made available. Hence, it is likely that our method constitutes a new entry for the synthesis of these valuable materials.

Acknowledgments

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Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749–6757.
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9. Colorless oil (bp 183–185 °C/10 mmHg); isolated by column chromatography (silica gel, petroleum ether/Et_2O 3:1). Spectral data in agreement with literature.[8a]
10. (a) Squalene 2,3(*S*)-oxide (**2a**): colorless oil; bp 164–165 °C/10 mmHg; $[\alpha]_D^{25}$ −1.3 (*c* 4.89, MeOH) (lit.:[7b] $[\alpha]_D^{23}$ −1.3, *c* 0.85, MeOH). Using chiral column HPLC [Chiralpak AS (25 cm × 0.46 cm id) hexane/*i*-PrOH 99/1, flow 0.8 mL/min] an ee of 92% was determined. Spectral data in agreement with literature[7b]; (b) Squalene 2,3(*R*)-oxide (**2b**): colorless oil; bp 164–165 °C/10 mmHg; $[\alpha]_D^{25}$ +1.0 (*c* 2.1, MeOH); ^1H NMR ($CDCl_3$, 500 MHz) *δ*: 512 (m, 5H), 2.70 (t, $J = 6.5$ Hz, 1H), 2.10–1.97 (m, 20H), 1.68 (s, 3H), 1.61 (s, 3H), 1.59 (s, 12H), 1.29 (s, 3H), 1.25 (s, 3H); $\{^1H\}^{13}C$ NMR ($CDCl_3$, 125 MHz) *δ* 135.1, 134.9, 133.9, 131.2, 124.9, 124.3, 124.2, 64.2, 58.3, 39.7, 39.6, 36.3, 28.2, 27.4, 26.7, 26.6, 25.7, 24.9, 18.7, 17.7, 16.0; HRMS (LDI,TOF): calcd for ($C_{30}H_{50}O+Na^+$): 449.3759, found: 449.3748; IR (neat): 2962, 2918, 2855, 1449, 1378 cm^{-1}. Using chiral column HPLC [Chiralcel OD (25 cm × 0.46 cm id) hexane/*i*-PrOH 98/2, flow 1.5 mL/min] an ee of 75% was determined.
11. (a) (*R*)-2,3-Dihydroxy-2,3-dihydrosqualene (**6a**): colorless oil; $[\alpha]_D^{25}$ +10.2 (*c* 1.97, $CHCl_3$) (lit.:[11c] $[\alpha]_D^{25}$ +10.7, *c* 1.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ*: 5.13 (m, 5H), 3.35 (dd, 1H, $J = 10.2$, 2.2 Hz), 2.03 (m, 20H), 1.67 (s, 3H), 1.62 (s, 3H), 1.60 (s, 12H), 1.19 (s, 3H), 1.16 (s, 3H); $\{^1H\}^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 135.1, 134.9, 134.8, 131.2, 125.1, 124.4, 124.2, 78.3, 73.0, 39.7, 39.6, 36.8, 29.6, 28.2, 26.7, 26.6, 26.4, 25.6, 23.2, 17.6, 16.0, 15.9; HRMS (EI, 70 eV): calcd for $C_{30}H_{52}O_2$: 444.3967, found: 444.3961; IR (neat): 3402, 2922, 1667, 1447, 1383, 1158, 1079, 847 cm^{-1}. Using chiral column HPLC [Chiralcel OD (25 cm × 0.46 cm id) hexane/*i*-PrOH 99/1, flow 1.5 mL/min] an ee of 95% was determined; (b) (*S*)-2,3-Dihydroxy-2,3-dihydrosqualene (**6b**): colorless oil; $[\alpha]_D^{25}$ −9.5 (*c* 1.4, $CHCl_3$) (lit.:[11c] $[\alpha]_D^{25}$ −10.7, *c* 1.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) *δ*: 5.13 (m, 5H), 3.35 (dd, $J = 10.2$ Hz, 2.2 Hz), 2.03 (m, 20H) 1.67 (s, 3H), 1.62 (s, 3H), 1.60 (s, 12H), 1.19 (s, 3H), 1.16 (s, 3H); $\{^1H\}^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 135.1, 134.9, 134.8, 131.2 125.1, 124.4, 124.2, 78.3, 73.0, 39.7, 39.6, 36.8, 29.6, 28.2, 26.7, 26.6, 26.4, 25.6, 23.2, 17.6, 16.0, 15.9; HRMS (EI, 70 eV): calcd for $C_{30}H_{52}O_2$: 444.3967, Found: 444.3959; IR (neat): 3402, 2922, 1667, 1447, 1383, 1158, 1079, 847 cm^{-1}. An ee 89% was determined by chiral column HPLC [Chiralcel OD (25 cm × 0.46 cm id) hexane/*i*-PrOH 99/1, flow 1.5 mL/min]; (c) Boar, R. B.; Damps, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 709–712.
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13. 2,3(*S*);22(*S*),23-Dioxide (**3a**): bp 183–185 °C/10 mmHg (lit.[14] 83 °C/0.03 mmHg); ^1H NMR ($CDCl_3$, 500 MHz) *δ*: 5.14 (m, 4H), 2.70 (t, 2H, $J_1 = 6.5$ Hz), 2.12–1.97 (m, 16H), 1.69–1.57 (m, 4H), 1.61 (s, 6H), 1.60 (s, 6H) 1.30 (s, 6H), 1.26 (s, 6H); $\{^1H\}^{13}C$ NMR ($CDCl_3$, 125 MHz) *δ*: 134.9, 133.9, 124.9, 124.3, 64.2 (HCO), 58.3 (CO), 39.7, 36.3, 28.2, 27.4, 26.6, 24.9, 18.7, 16.0. IR (neat): 2960, 2929, 2848, 1450, 1378, 1260, 1121, 1082, 1026, 800 cm^{-1}; HRMS (LDI,TOF): calcd for ($C_{30}H_{50}O_2+K^+$): 481.3448, found: 481.0662 ($M+K^+$); $[\alpha]_D$ −2.2 (*c* 1.8 $CHCl_3$); *de* > 98%, as determined by chiral column HPLC (Chiralcel OD, 25 cm × 0.46 cm id, eluent hexane/*i*-PrOH 98/2, flow 1.5 mL/min).
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