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STEREOCHEMISTRY OF ALLENIC COMPOUNDS

ABSOLUTE CONFIGURATION OF CYCLOALLENOLS AND CYCLOALLENONES[1]

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Abstract—The absolute configuration of α-cycloallenols (3 and 4) as well as of α-cycloallenones (1) has been correlated to that of cyclic alkenols (2) by chemical transformations.

Résumé—La configuration absolue des α-cycloallénones (1) et des cycloallénols (3 et 4) a été déterminée grâce à une filiation chimique avec les alcools cycliques (2).

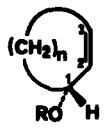
Recently, a straightforward synthesis of racemic as well as optically active α-cycloallenones (1) was reported.[2] (−)-2,3-Cyclononadien-1-one (1a) and (−)-2,3-cycloundecadien-1-one (1b) were prepared from (−)-2-cyclooctен-1 ol (2a) and (−)-2-cyclodecen-1-ol (2b) by this process. It was of interest to assign the absolute configuration to these keto allenes (1) because they are the first optically active allenones obtained, in which the chirality is due solely to the allene moiety. A few optically active α-allenones have been described in the literature, for example in the steroid series,[3] but they possess chiral centers and axes, and therefore differ from system (1), precluding comparison of their chemical and physical properties. The determination of the absolute configuration of the α-cycloallenones (1) was problematical as unambiguous correlations were not possible. Due to the limited number of chiral propadienes in which the absolute configuration has been determined in an unambiguous way, there is no established general relationship between the configuration and the physical properties of allenes.[4] Chemical methods based on stereoselective transformations of axial to central chirality have been published, but unfortunately they have certain limitations.[4-6] In many cases the degree of stereoselectivity of the transformation can, at best, be estimated only approximately. Optical rotations applying the empirical rules proposed by Lowe et Brewster[7] and circular dichroism[8] have been used in a limited number of cases, but can be misleading.[6,9] Furthermore, theoretical treatments predicting the Cotton effects exhibited by chiral allenes have been developed from *ab initio* calculations, but they do not appear to be generally applicable[10] or accurate.[11] Moreover, the above methods have been applied mainly to linear compounds and not to cyclic allenes.

It has been shown previously[2] that manganese dioxide oxidation of the diastereomeric alcohols (3 and 4) proceeds with different rates. Since the allenol (3b) could not to be separated from its isomer (4b), for a conversion of 20–30%, it can be assumed that only alcohols (3) are transformed to ketones (1). Oxidation of the allenol (3b) to the 2,3-cycloundecadien-1-one (1b) followed by reduction with lithium aluminium hydride gave back the alcohol (3b), thus showing that the propadiene unit is not isomerized or racemized during the process. Since the allenic chirality was preserved during the oxidation of alcohols (3) to ketones (1), the absolute configuration and optical purity of the allenic ketones can be deduced from those of the alcohol precursors. Additionally, since the relative configuration of the diastereomeric alcohols (3) and (4) has been established previously by chemical means and confirmed by X-ray analysis of the phenylurethane derivative (5)[12] the absolute stereochemistry of the allene unit can be correlated to that of the asymmetric carbinolic carbon atom. This can be achieved by assigning the configuration of the allylic alcohols (2) at position 1, as the asymmetric carbon atom (C_1) is not affected by the changes involved in the synthetic conversion of alcohols (2) to the allenic alcohols (3 and 4).

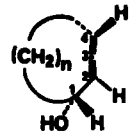
Partial kinetic resolution of chiral secondary alcohols is a straight-forward technique used to establish their absolute configuration.[13] It has been shown that the empirical rule proposed by Horeau holds for allylic,[14] propargylic[14,15] and benzylic[16] alcohols in which the unsaturated moiety must be considered bulkier than an alkyl group. When applied to 2-cycloocten-1-ol (2a) and 2-cyclodecen-1-ol (2b) this rule indicates the *R*(−)-configuration. This assignment was confirmed by chemical transformation of the cyclic allylic alcohols (2) to the corresponding *S*(+)-2-octanol (9a) and *S*(+)-2-decanol (9b) of known stereochemistry.

In order to perform this chemical conversion, the OH group in alcohols 2a and 2b was protected as the tetrahydropyranyl ether derivative to give the ethers 2c and 2d, respectively. Ozonolysis of the double bond in the cyclic compounds (2c) and (2d), followed by reductive treatment of the ozonide, furnished the ether diols (6). Conversion of the diols (6a and 6b) to the corresponding ditosylates (7a and 7b) by treatment with *p*-toluenesulphonyl chloride in pyridine solution, was followed by reduction with LAH to afford the ethers (8). Removal of the protecting group by acid hydrolysis yielded the corresponding 2-alkanols (9). More specifically, the above outlined transformation of (−)-2-cycloocten-1-ol (2a) and (−)-2-cyclodecen-1-ol (2b) provided *S*(+)-2-octanol (9a) and *S*(+)-2-decanol (9b)[17] respectively. Thus the *R*(−) absolute configuration was assigned unambiguously to the allylic alcohols (2). Both compounds (2)

1 a, n = 5
b, n = 7



2 a, R = H, n = 5; c, R = THP n = 5
b, R = H n = 7; d, R = THP, n = 7



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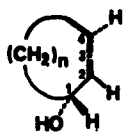

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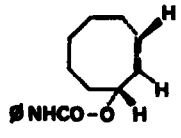

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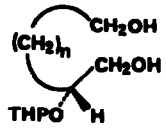

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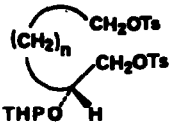

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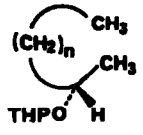

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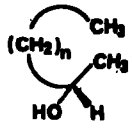

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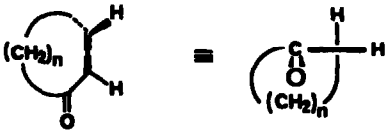

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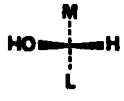

M: medium sized group

L: large sized group

11

give α-cycloallenols (3a and 3b) in the *Ra*R(+) form, and 4a in the *Ra*S(−) form, by the described procedure. Oxidation of the hydroxy-derivatives (3a and 3b) thus afforded the corresponding R(−)-cycloallenones (1a and 1b).

After assigning the absolute configuration to the α-cycloallenols (3 and 4) and the cycloallenones (1) it was of interest to examine their chiroptical properties.

The Lowe–Brewster rule does not seem to be applicable to α-cycloallenols because of the presence of an asymmetric C atom which makes an unknown contribution to the rotatory power at 589 nm. Application of the rule to α-cycloallenones, however, should be possible. In fact, this method predicts the correct R(−)-configuration for these compounds. It is worth mentioning, however, that while 2,3-cyclononadien-1-one (1a) obeys the Lowe–Brewster rule, 1,2-cyclonadiene is a well known exception.[9]

The circular dichroism (CD) curve of R(−) 1a displays two Cotton effects i.e. an intense negative Cotton effect at 254 nm ([θ] − 18.500), and a second positive Cotton effect at 229 nm ([θ] + 14.220). The CD curve of R(−) 1b has a similar shape with a negative Cotton effect at 254 nm ([θ] − 8.200) and a positive shoulder at 218 nm ([θ] + 1.880). Although the coupled oscillators theory has been invoked to explain the chiroptical properties of some allenic acids and hydrocarbons,[10,18,19] *a priori* this theory is not relevant for the interpretation of the Cotton effects exhibited by cycloallenic ketones because, first, of their cyclic nature and, secondly but mainly, of the presence of a carbonyl group conjugated to the propadiene unit. The quadrant rule[8] suggested for the propadiene chromophore cannot be extrapolated to allenones, which obviously constitute another chromophoric group, because it presents an entirely different electronic pattern.

The partial kinetic resolution method[13] was applied successfully to the allylic alcohols (2). Thus, it was of interest to investigate whether or not this technique would be applicable to the allenols (3 and 4). The kinetic resolution of racemic alcohols (3a and 4a) was performed with (+)α-phenylbutyric anhydride. The resulting mixture was carefully separated and both residual allenols (3a and 4a) were shown to be dextrorotatory. Hence, since (+)α-phenylbutyric anhydride was used, the residual alcohol has the absolute configuration shown in structure 11.[13] If the allene unit can be considered "larger" than an alkyl group as in the case of a vinyl or ethynyl unit, the configuration of the allenols (3a and 4a) should be *Ra*R(+) and *Ra*S(+) respectively. This result is in contradiction with the aforementioned experimental observations which unambiguously assigned the *Ra*S(−) configuration to alcohol 4a. Interestingly the optical

yields (2–4%) for the kinetic resolution of the α-cycloallenols (3a and 4a) are much lower than those usually obtained with allylic alcohols. This can be readily accounted for, however, if there is only a slight difference in the steric and electronic effects of a methylene chain and the propadiene unit.

In conclusion the absolute stereochemistry of the α-cycloallenones (1) as well as the cycloallenols (3 and 4) has been assigned by chemical correlation with that of the parent allylic alcohols (2). Unfortunately, the chiroptical and kinetic resolution techniques which provide useful information in many areas of organic chemistry, meet some difficulties when applied to allenic derivatives.

EXPERIMENTAL

IR spectra were recorded on a Beckmann Acculab 4 instrument in film or in CCl_4 soln. UV spectra were taken in EtOH soln on a Beckmann DBT spectrophotometer. NMR spectra were recorded at room temp on a 60 MHz JEOL PMX60 spectrometer, with $CDCl_3$ containing TMS as an internal standard, except for trimethylsilyl derivatives, where $CHCl_3$ was used (δ $CHCl_3$ = 7.24 ppm). Resonance frequencies are quoted in ppm downfield from the TMS and are accurate to ±0.01 ppm. Coupling constants, J, expressed in hertz (Hz) are accurate to ±1 Hz; d, doublet; t, triplet; q, quartet; m, multiplet. M.ps were determined with a Bücchi-Tottoli apparatus and are not corrected. Microanalyses were done by the CNRS, Lyon. Mass spectra were recorded on a Varian MAT CH5 spectrometer by the "Service de Spectrométrie de Masse" in Lyon. Optical rotations were determined in CH_2Cl_2 soln at room temp. on a Perkin Elmer Model 141 spectropolarimeter. GLC analyses were obtained on a Carlo Erba Fractovap chromatograph, equipped with a Carbowax 20M 10% chromosorb WAW column, or a DEGS 25% chromosorb WAW column; N_2 carrier at a 20 ml/min flow rate. Circular dichroism (CD) curves were recorded in methanol soln on a Jouan 3 dichrograph. The assistance of Mme Martin Borret is acknowledged.

2,3-Cyclononadien-1-ols (3a *and* 4a). The preparation of these alcohols has been described previously,[2] from 2-cycloocten-1-ol ($[\alpha]_D$ −48°). CD: 3a, $\Delta\epsilon_{229}$ +2.82, $[\theta]_{229}$ +9,207; 4a, $\Delta\epsilon_{219}$ −2.75, $[\theta]_{219}$ −9,100.

(−)-2,3-Cyclononadien-1-one (1a). This was obtained by MnO_2 oxidation of 3a by the known procedure.[2] CD: $\Delta\epsilon_{254}$ −5.3, $[\theta]_{254}$ −18,500; $\Delta\epsilon_{229}$ +4.3, $[\theta]_{229}$ +14,220.

(−)-2-Cyclodecen-1-ol. (2b). 2-Cyclodecen-1-ol was resolved through the camphanate ester, as previously described for 2-cycloocten-1-ol.[2] The camphanate of 2b showed: m.p. 144–145°; $[\alpha]_D$ −92° (c = 2). IR: 1780 1750 1720 cm^{-1}. NMR: δ 5–6 (m, 2H), 1–2 (m 19H), 1.05 (s, 3H), 1.0 (s, 3H), 0.9 ppm (s, 3H). (Found: C, 72.10; H 9.10. $C_{20}H_{30}O_4$ requires: C, 71.85; H 8.96%).

To 3 g LAH in 300 ml anhyd ether, 2.9 g camphanate of 2b in 170 ml anhyd ether were added dropwise with stirring at −20°. Stirring was continued for 1.5 hr to reach room temp. After the usual work-up, 1.35 g alcohol (2b) was obtained. This material was identical with the starting racemic alcohol, except for the rotation: $[\alpha]_D$ −77.5° (c = 1.5). 20 mg of the optically active alcohol were acetylated (Ac_2O, pyridine at room temp. overnight). The NMR spectrum of the acetate in the presence of Eu (t facam)$_3$[20] exhibits a single signal for the acetyl group under conditions in which the racemic acetate shows two signals of equal intensity. Optical purity of compound 2b is estimated to be at least 95%.

2,3-Cycloundecadien-1-ols (3b *and* 4b). A mixture containing 2b (1.3 g) in 6 ml 50% NaOH aq and 40 ml cetyltrimethylammonium chloride was vigorously stirred. Then 10 g of freshly distilled bromoform were slowly added. Stirring was continued for 4 hr. After usual work-up, 1.3 g (47% yield) 11,11-dibromobicyclo[8.1.0] undecan-2-ol was isolated and shown to be identical with the racemic material,[2] except for the rotation: $[\alpha]_D$ −56° (c = 0.5).

Silylation under the usual conditions (excess Me_3SiCl in dry pyridine at room temp. for 30 min) yields 1.4 g (88%) of the trimethylsilyl ether $[\alpha]_D$ −22° (c = 0.4). IR (film): 1400 1370 1250 cm^{-1}. NMR: 3.6 (m, 1H), 1–2 (m, 16H), 0.2 ppm (s, 9H). (Found: C, 42.97; H, 6.58; Br, 39.96. $C_{14}H_{26}OBr_2Si$ requires: C, 42.21; H, 6.53; Br, 40.20%).

300 mg (7.55×10^{-4} m) of this silyl ether in anhyd ether soln, at −90°, under N_2 were treated with 0.38 ml (7.55×10^{-4} m) MeLi in ether. The temp was allowed to reach −20°. The mixture was quenched with water and usual work-up afforded 200 mg (100%) of the TMS ethers of 2,3-cycloundecadien-1-ols. The crude mixture was hydrolyzed with aqueous MeOH at room temp to give quantitatively 3b (90%) and 4b (10%), which were shown to be identical with the corresponding racemates.[2] $[\alpha]_D$ +15° (c = 0.6). Alcohols (4b) could not be separated completely from its isomer. This mixture was used for the next step without separation.

(−)-2,3-Cycloundecadien-1-one (1b). A soln containing 100 mg of the mixture of 3b and 4b in 20 ml CH_2Cl_2 was treated for 5 min with 1 g MnO_2 at room temp. The mixture was filtrated on a silica gel column, then chromatographed on preparative silica gel plate, to yield 17 mg (18%) of 1b showing spectroscopic properties identical with those of the racemate. $[\alpha]_D$ −6.7° (c = 1.7), $[\alpha]_{578}$ −8.0°, $[\alpha]_{546}$ −12.7, $[\alpha]_{436}$ −74.2, $[\alpha]_{365}$ −480°. CD: $\Delta\epsilon_{254}$ −2.48, $[\theta]_{254}$ −8,200; $\Delta\epsilon_{218}$ +0.57, $[\theta]_{218}$ +1,880.

Kinetic esterification of (−)-2-cyclooctenol (2a). A mixture of 63 mg (5×10^{-4} m) of 2a ($[\alpha]_D$ −30°) and 310 mg (10^{-3} m) of racemic α-phenylbutyric anhydride in 1.5 ml pyridine, was stirred for 1 hr at room temp. Then 1 ml water was added with cooling and the mixture was stirred for 1 additional hr. After that time, 2 ml benzene and 2 ml water were added and the acidity was titrated with normal NaOH (1.6 ml). The aqueous layer was separated and extracted with benzene, then acidified with dil aq HCl. Phenylbutyric acid was extracted (benzene), washed and dried: $[\alpha]_D$ +6.5°. Esterification yield: 80%. Optical yield: 16.7%.

Kinetic esterification of cis*-2-cyclodecen-1-ol* (2b). Following the same procedure, 77 mg (5×10^{-4} m) of 2b ($[\alpha]_D$ −53°) was treated by 310 mg α-phenylbutyric anhydride. After hydrolysis, titration (N NaOH 1.6 ml), and extraction the acid showed $[\alpha]_D$ +3.5°. Esterification yield: 80%. Optical yield: 10%.

Correlation of the alcohols (2) *with the* S(+)−*2-alkanols* (9)

(a) *2-Cycloocten-1-ol* (2a). A soln containing 378 mg (3×10^{-3} m) of partially resolved ($[\alpha]_D$ −10°) (2a), 260 mg (3.1×10^{-3} m) of dihydropyranne, and a crystal of *p*-toluene-sulphonic acid was stirred for 1 hr at room temp. After addition of ether, and 10% $NaHCO_3$ aq, the organic layer was separated, washed to neutrality dried over $MgSO_4$ and evaporated. There was obtained 600 mg (95%) of the tetrahydropyranyl derivative of 2a as an oil. IR: 1140 1120 cm^{-1}. NMR: δ 5.5 (m, 2H), 4.7 (m, 2H), 3.5–3.8 (m 2H), 1.5 ppm (m, 16 H).

A soln of 440 mg of this oil in 10 ml MeOH was ozonized at −60°. After completion of the reaction, the solvent was evaporated and 10 ml of dry THF was added. The resulting soln was treated with LAH (220 mg) in 50 ml THF, then the mixture was refluxed for 4 hr, until the KI ozonide test was negative. The mixture was then worked up as usual to afford 160 mg of 6a; IR: 3360 1140, 1120 cm^{-1}; NMR: 2 broad multiplets (*ca.* 3.7–3.3 and 2.1–1.8 ppm). The diol ether (6a) in 1 ml pyridine was tosylated overnight with 280 mg *p*-toluenesulphonyl chloride at 0° under stirring. The mixture was hydrolyzed, extracted with CH_2Cl_2, and the aqueous layer was washed to neutrality, dried ($MgSO_4$) and evaporated. The ditosylate-ether (7a; 300 mg, 85%) was obtained as a liquid: [IR: 1600, 1400, 1170 cm^{-1}; NMR: δ7.6 (d, 4H), 7.3 (d, 4H), 4.0 (m 6H), 2.45 (s, 6H), 1.2–1.5 ppm. (m, 18H)], which was used for the next step without purification.

A mixture of 7a (300 mg) and 1 g LAH in 40 ml anhyd ether was stirred for 24 hr at room temp. The mixture was hydrolyzed and then worked up as usual. The crude product was purified on a silica gel column to yield 80 mg of the tetrahydropyranyl derivative of 2-octanol (8a; 70%). This ether was hydrolyzed (AcOH: H_2O, 7:3) to give *S*(+)-2-octanol (9a): $[\alpha]_D$ +1.5° (c = 0.5).

(b) *2-Cyclodecen-1-ol* (2b). The same procedure was used with

the alcohol (−) (2b): $[\alpha]_D - 38°$, to provide 6b: IR: 3360, 1140, 1120 cm^{-1}; NMR: δ 3.5 (m, 10H), 2.0–1.5 ppm (m, 20H), and 7b: IR: 1600, 1400, 1180, 1140, 1120 cm^{-1}; NMR: δ 7.8 (d, 4H), 7.3 (d, 4H), 4.0 (m, 6H), 2.45 (s, 6H), 1.5–1.2 ppm (m, 22H). Reduction of 7b, followed by the acid hydrolysis of the ether group gave S(+)-9b: $[\alpha]_D + 3°$ ($c = 0.5$).

Kinetic resolution of 2.3-*cyclononadien*-1-*ol* (3a). A mixture of 181 mg (1.31×10^{-3} m) of racemic 3a 203 mg (0.655×10^{-3} m) α-phenylbutyric anhydride (dextrorotary, 81% e.e.) in 1 ml pyridine was stirred for 4hr, then hydrolyzed with 1 ml water. After one additional hr, 1 ml water and 1 ml benzene were added, and the mixture was titrated with N/10 NaOH (8.45 ml). The organic layer was separated, washed, dried over $MgSO_4$ and evaporated. The mixture was chromatographed on a silicagel column. The residual allenol (69 mg; 3a) was obtained as an oil: $[\alpha]_D + 4.1°$. Esterification yield: 71%. Optical yield: 4.2%.

Kinetic resolution of 2.3-*cycloundecadien*-1-*ol* (4a). Following the same procedure from 100 mg racemic 4a, 37.4 mg of partially resolved 4a were obtained: $[\alpha]_D + 0.605°$. Esterification yield: 68.5%. Optical yield: 2.4%.

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