1,5-Acyclic stereoselection. The stereocontrolled synthesis of optically active vitamin E fourteen-carbon side chain alcohol[1]

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The Diels–Alder product **3** was first transformed into the symmetrical nine-membered cyclic carbonate **8**. Reaction of **8** with *l*-(−)-α-methylbenzylamine (**12**) yielded a mixture of optically active diastereoisomeric urethanes **9***a* (**9**, R = H, R′ = $C_6H_5CHCH_3NHCO$—) and **9***b* (**9**, R = $C_6H_5CHCH_3NHCO$—, R′ = H) which were separated and respectively converted into **11***a* and **11***b*. Compounds **11***a* and **11***b* were then transformed respectively into the optically active side chain alcohol **2** (R = H) of vitamine E (**1**).

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Le produit de Diels–Alder **3** fut transformé en carbonate symétrique cyclique à neuf membres **8**. La réaction de **8** avec la *l*-(−)-α-méthylbenzylamine a donné les uréthanes diastéréoisomériques optiquement actifs **9***a* (**9**, R = H, R′ = $C_6H_5CHCH_3$-NHCO—) et **9***b* (**9**, R = $C_6H_5CHCH_3NHCO$—, R′ = H) qui furent séparés et respectivement transformés en composés **11***a* et **11***b*. Ces derniers ont conduit par la suite à la chaîne latérale de la vitamine E, i.e. l'alcool **2** (R = H) optiquement actif.

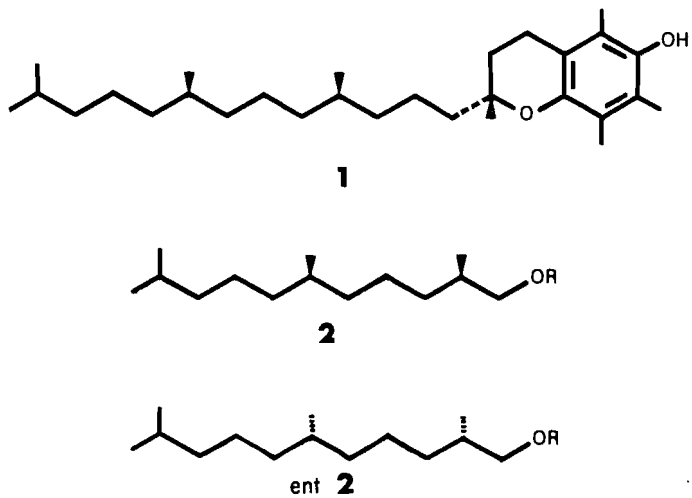
The stereocontrolled synthesis of substituted aliphatic chains containing chiral centers, i.e. acyclic stereoselection, is presently an active field of research (1). For instance, several groups have reported (2, 3) various ways of constructing the 1,5-dimethylated aliphatic chain which is found in vitamin E (**1**) (Scheme 1) and in several other natural products like vitamin **K**, phytol, and insect pheromones (pine saw fly (4) and tsetse fly (5)).

In this communication, we wish to report a new strategy for the synthesis of the optically active side chain alcohol **2** (R = H) which has been converted into vitamin E (2).

The Diels–Alder product **3** (mp 94–95°C) which is readily available (6) from the addition of maleic anhydride to *trans,trans*-2,4-hexadiene, was chosen as starting material (Scheme 2). Esterification of **3** (CH_3OH, HCl, 95% yield) gave the *cis*-dimethylester **4**[3] (mp 49–50°C) which was converted ($CHBr_3$, NaOH, $(C_2H_5)_3NCH_2C_6H_5Cl$, 0° → 25°C, 65% yield) (7) into the dibromocyclopropane derivative **5** (mp 114–115°C). Basic hydrolysis (NaOH, H_2O–dioxane–CH_3OH, 99% yield) of **5** gave the corresponding dicarboxylic acid which upon bis-decarboxylation ($Pb(OAc)_4$, pyridine, 65°C, 84% yield) (8) yielded the cyclic olefin **6**. Cleavage of **6** ((a) O_3, CH_3OH, CH_2Cl_2, −78°C (9) and (b) $LiBH_4$, 0°C, 96% yield) gave the *meso*-dibromocyclopropyldiol **7** (mp 126–127°C).

Compound **7** was then converted ((a) dihydropyran, *p*-TsOH, C_6H_6, 84% yield, (b) CH_3Li, ether, −35°C, 96% yield (10)) into the allene derivative **10** (R = R′ = THP). Catalytic reduction (H_2, PtO_2, CH_3OH, 99% yield) and hydrolysis (*p*-TsOH, CH_3OH, 89%) of **10** (R = R′ = THP) gave *meso*-2,6-dimethylheptan-1,7-diol **11** (R = R′ = H) (3*f*).

A toluene solution of phosgene was slowly added (with a syringe pump) during a period of 10 h to a mixture of *meso*-dibromocyclopropyldiol **7**, triethylamine, and dichloromethane, to yield the nine-membered cyclic carbonate **8** (mp 96–98°C) in 80% yield (11). The lithiated derivative of *l*-(−)-α-methylbenzylamine (**12**) (*n*-BuLi, ether) was then reacted with the symmetrical cyclic carbonate **8** (THF, −78°C, 30 min, 86% yield) to yield a mixture (~1:1 ratio) of optically active diastereoisomeric urethanes **9***a* (**9**, R = H and R′ = Ur = $C_6H_5CHCH_3NHCO$—) and **9***b* (**9**, R = Ur = $C_6H_5CHCH_3$-NHCO— and R′ = H) which were separated by hplc (12). Treatment of optically active urethane **9***a* with methyllithium (ether, −35°C, 99% yield) (10) gave the corresponding allene **10***a* which on catalytic reduction (H_2, PtO_2, CH_3OH, 98% yield) furnished the optically active urethane **11***a*. Similarly, **9***b* yielded the optically active urethane **11***b* via **10***b*.



SCHEME 1

Each diastereoisomer (**11***a* and **11***b*) was then respectively converted into optically active **2** (R = H), i.e. 2*R*,6*R*,2,6,10-trimethylundecan-1-ol. The conversion **11***a* (**11**, R = H, R′ = Ur) → **2** (R = H) was carried out in the following manner: (a) *p*-TsCl, $(C_2H_5)_3N$, CH_2Cl_2, 0° → 25°C, 99% yield in tosylate **11** (R = Ts, R′ = Ur), (b) $SiHCl_3$, $(C_2H_5)_3N$, C_6H_6, 25°C (13), 76% yield in tosylate alcohol **11** (R = Ts, R′ = H; $[\alpha]_D$ +8.07° (*c* 3.025 in $CHCl_3$), (c) dihydropyran, pyridinium *p*-toluenesulfonate (PPTS), CH_2Cl_2 (14), 94% yield in THP derivative **11**

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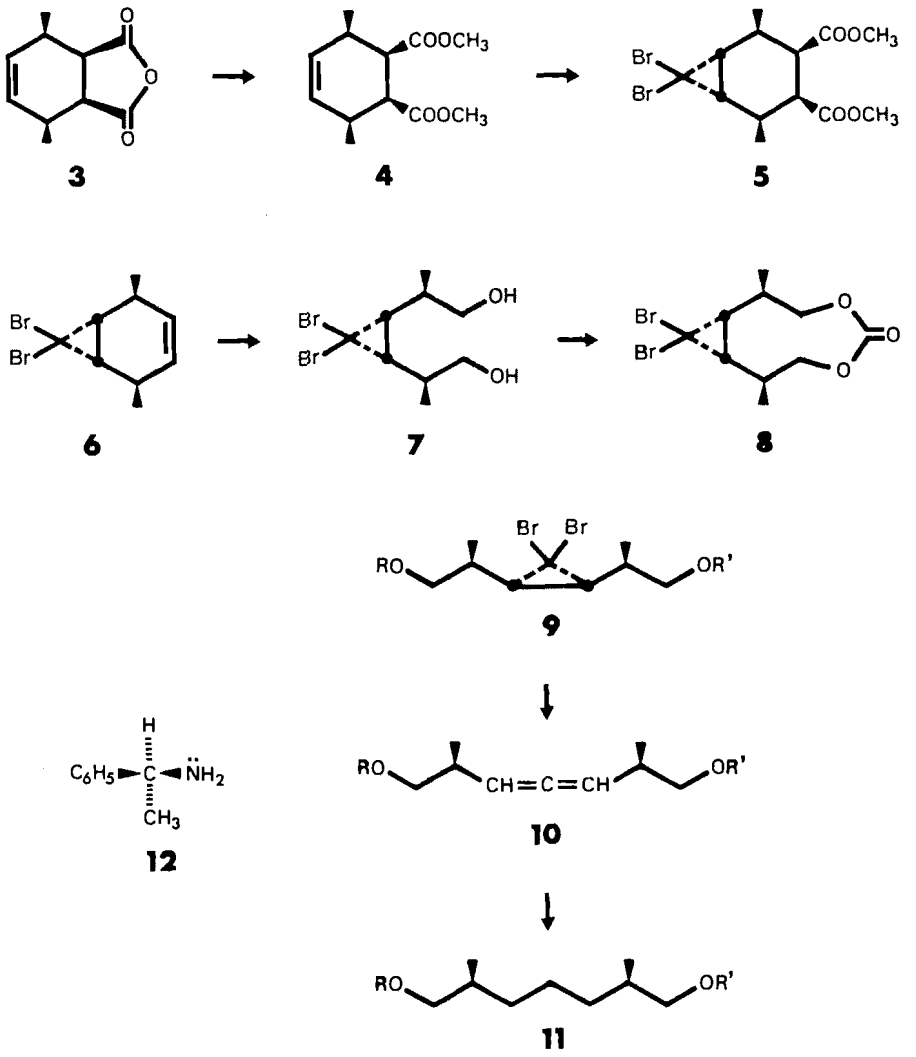
[3]For all new substances, the spectra (ir, 250 MHz and 60 MHz ^1H nmr, ^{13}C nmr, and high resolution mass spectra) were in complete agreement with the assigned structures.



SCHEME 2

(R = Ts, R′ = tetrahydropyran), (d) $(CH_3)_2CHCH_2CH_2MgBr$, Li_2CuCl_4, THF, −78° → 25°C (15; for preparation of the reagent, see ref. 15*b*), 60% yield in **2** (R = THP), and (e) CH_3OH, PPTS, (14), 99% yield in **2** (R = H). The transformation **11***b* (**11**, R = Ur, R′ = H) → **2** (R = H) was realized via the following steps: (a) *tert*-butyldimethylsilyl (TBDMS) chloride, imidazole, THF, 25°C (16), 96% yield in **11** (R = Ur, R′ = TBDMS), (b) $SiHCl_3$, $(C_2H_5)_3N$, C_6H_6, 25°C (13), 84% yield in **11** (R = H, R′ = TBDMS), (c) *p*-TsCl, $(C_2H_5)_3N$, CH_2Cl_2, 0° → 25°C, 90% yield in **11** (R = Ts, R′ = TBDMS), (d) $(CH_3)_2CHCH_2CH_2MgBr$, Li_2CuCl_4, THF, 0° → 25°C (15), 65% yield in **2** (R = TBDMS), and (e) $(n\text{-}Bu)_4NF$, THF, 25°C (16), 68% yield in **2** (R = H).

The diastereoisomer **11***b* (**11**, R = Ur, R′ = H) was also transformed into the enantiomer of **2** (R = H) (ent-**2**) (17), i.e. 2*S*,6*S*,2,6,10-trimethylundecan-1-ol, in the following way: (a) *p*-TsCl, $(C_2H_5)_3N$, CH_2Cl_2, 0° → 25°C, 86% yield in **11** (R = Ur, R′ = Ts), (b) $SiHCl_3$, $(C_2H_5)_3N$, C_6H_6, 25°C (13), 87% yield in **11** (R = H, R′ = Ts; $[\alpha]_D$ −8.05° (*c* 3.3 in $CHCl_3$), (c) *tert*-butyldimethylsilyl chloride, imidazole, THF, 25°C (16), 88% yield in **11** (R = TBDMS, R′ = Ts), (d) $(CH_3)_2CHCH_2CH_2MgBr$, Li_2CuCl_4, THF, 0° → 25°C (15), 66% yield in ent-**2** (R = TBDMS), and (e) $n(Bu)_4NF$, THF, 25°C (16), 83% yield in ent-**2** (R = H).

The samples of 2*R*,6*R*,2,6,10-trimethylundecan-1-ol (**2**, R = H, $[\alpha]_D$ + 8.6° (*c* 2.07, hexane) obtained and that of its enantiomer (ent-**2**, R = H, $[\alpha]_D$ −8.17° (*c* 2.09, hexane) (lit. (2, 3) $[\alpha]_D$ 8.6 ± 0.6°) were shown to be enantiomerically pure by analysis (250 MHz ^1H nmr) of their corresponding Mosher's ester derivative (O-methylmandelate) (18).

The principal elements of the above synthetic strategy can be summarized as follows: (a) The readily available symmetrical Diels–Alder product **3** ensures a complete control of the relative stereochemistry of the two methyl groups. (b) Appropriate functional group modifications and insertion of a methylene group (cyclopropane and allene formation and catalytic reduction) allow the mutation from a 1,4 to a 1,5-acyclic stereoselection process. (c) The symmetrical properties of **3** permit the formation of the nine-membered cyclic carbonate **8**. (d) Reaction of the symmetrical carbonate **8** with optically active *l*-(−)-α-methylbenzylamine gave a mixture of two optically active diastereoisomers which can be separated and converted into the desired optically active fourteen-carbon side chain alcohol **2**. This last operation ensures a complete control of the absolute configuration without loss of enantiomeric materials (12).

Work is now in progress to produce more complex substituted aliphatic chains starting from compounds **9** and **10**.

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