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A Short Enantioselective Synthesis of (+)-Sterpurene: Complete Intramolecular Transfer of Central to Axial to Central Chiral Elements[1]

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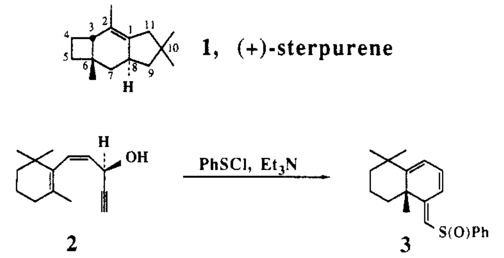
Sterpurene (**1**), the parent member of a novel class of sesquiterpenes possessing the unusual 4/6/5 ring system, has been isolated from the fungus *Stereum purpureum*, the metabolites of which are considered to be the causitive agents of the so called silver leaf disease.[2,3] This substance and related metabolites have been the subject of synthetic[2] as well as biosynthetic studies,[3] the latter being of particular interest due to the unusual mode of biosynthesis of this class of natural products.[3e,f] It is the purpose of this communication to demonstrate the use of a completely stereoselective vinylallene intramolecular Diels–Alder reaction[4] as the key step in an exceptionally concise, enantioselective synthesis of (+)-sterpurene (**1**).

Recently, we reported the transformation of dienynol **2** to the decalin system **3**.[5a] The central chiral element of **2** is considered to be transferred stereoselectively via a [2,3]-sigmatropic shift to the axial chiral element of an intermediate allene followed by transfer of the axial chiral element to the central chiral element in **3** via an electrocyclic process. This represents the only previous definitive example of the complete transfer of central chiral elements via an axial chiral element.[5b,c,6] As illustrated in Scheme II, we reasoned that if dienynol **4** were prepared in optically active form, then its central chiral element should be transferred to the axial chiral element of allene **6**[6] and subsequently to the two central chiral elements of **7** in an entirely enantio- and diastereoselective fashion. A particularly desirable feature of this approach is that vinylallenes such as **6** are topographically and sterically ideally set up for undergoing a completely selective exo intramolecular Diels–Alder addition to produce the hydrindane system.[7] The anticipated facility of this particular kind of cycloaddition was important since the thermal sensitivity of vinylallene sulfoxides[6] usually demands avoidance of excessive heating.

Scheme I



The synthesis of natural (+)-sterpurene (**1**) is given in Scheme III. Readily available 2,2-dimethyl-4-pentenal[8] was treated with lithium acetylide[9] to give racemic propargyl alcohol **8** in 97% yield.[10] Enantiomerically pure propargyl alcohol **9b**, $[\alpha]_D$ −8.1 (*c* 4.00, $CHCl_3$), prepared in two steps via Pirkle's chromatographic resolution method,[11-14] was coupled[15] with 1-iodo-2-methylcyclobutene (**10**)[16] to give dienynol **4**, $[\alpha]_D$ −13.2 (*c* 9.10, $CHCl_3$). We were delighted to find that treatment of **4** with phenylsulfenyl chloride in methylene chloride (*room temperature*, 38 h) afforded the desired cyclized product **7** [as a 61:39 mixture of sulfoxide diastereomers: major, less polar isomer, $[\alpha]_D$ −110.4 (*c* 1.25, $CHCl_3$); minor, more polar isomer, $[\alpha]_D$ −14.0 (*c* 1.10, $CHCl_3$)] in 70% yield. Unlike related systems, vinylallene **6** does not undergo a competing [1,5]-hydrogen shift.[17]

Transformation of sulfoxide **7** to diene **11**,[18] $[\alpha]_D$ −49.2 (*c* 1.25, $CHCl_3$), followed by dissolving metal reduction[19] afforded

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(1) Portions of this study were reported at the First Princess Chulabhorn Science Congress, International Congress on Natural Products, Bangkok, Thailand, December, 1987.

(2) Synthesis of racemic sterpurene: (a) Murata, Y.; Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1981**, *22*, 4313. (b) Möens, L.; Baizer, M. M.; Little, R. D. *J. Org. Chem.* **1986**, *51*, 4497. (c) Synthesis of racemic sterpuric acid: Paquette, L. A.; Lin, H.-S.; Coghlan, M. J. *Tetrahedron Lett.* **1987**, *28*, 5017. (d) For synthesis of a related sesquiterpene (sterepolide), see: Trost, B. M.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1985**, *107*, 4586.

(3) (a) Ayer, W. A.; Saeedi-Ghomi, M. H. *Can. J. Chem.* **1981**, *59*, 2536. (b) Ayer, W. A.; Saeedi-Ghomi, M. H. *Tetrahedron Lett.* **1981**, *22*, 2071. (c) Ayer, W. A.; Saeedi-Ghomi, M. H.; Van Engen, D.; Tagle, B.; Clardy, J. *Tetrahedron* **1981**, *37*, Supplement No. 1, 379. (d) Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199. (e) Ayer, W. A.; Nakashima, T. T.; Saeedi-Ghomi, M. H. *Can. J. Chem.* **1984**, *62*, 531. (f) Abell, C.; Leech, A. P. *Tetrahedron Lett.* **1987**, *28*, 4887.

(4) Intramolecular vinylallene Diels–Alder reaction: (a) Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370. (b) Reich, H. J.; Eisenhart, E. K.; Olson, R. E.; Kelly, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 7791. (c) Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487. (d) For a biosynthetic proposal involving this process, see: Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631. (e) For a recent review of intramolecular Diels–Alder reactions, see: Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.

(5) (a) Okamura, W. H.; Peter, R.; Reischl, W. *J. Am. Chem. Soc.* **1985**, *107*, 1034. (b) For examples of the intramolecular transfer of a central chiral element to an axial chiral element, see ref 6 and: Meyers, A. I.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 1135 and references cited therein. (c) For a discussion of stereochemical nomenclature, see: Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.

(6) In our experience, the pericyclic transformations (e.g., the sulfenate ester–sulfoxide rearrangement) of chiral propargyl alcohols to chiral allenes represent the most reliable approach for achieving complete enantioselectivity in the preparation of allenes. (a) Braverman, S.; Stabinsky, Y. *Isr. J. Chem.* **1967**, *5*, 125. (b) Smith, G.; Stirling, C. J. M. *J. Chem. Soc. C* **1971**, 1530. (c) Cinquini, M.; Colonna, S.; Cozzi, F.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. I* **1976**, 2061.

(7) Preliminary experiments in our laboratory have indicated that the intramolecular Diels–Alder reaction of vinylallene sulfoxides (possessing a two carbon tether at the allenic terminus to the dienophile component as in **6**) leading to hydrindane systems is especially facile (K. Bartels, unpublished results). Snider has reported the only other similarly facile example of an intramolecular vinylallene Diels–Alder reaction leading to a hydrindane system.[4a]

(8) (a) Brannock, K. C. *J. Am. Chem. Soc.* **1959**, *81*, 3379. (b) Salomon, R. G.; Ghosh, S. *Org. Synth.* **1984**, *62*, 125.

(9) Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250.

(10) All new compounds exhibited appropriate ^1H and ^{13}C NMR, IR, and exact mass and low resolution MS data.

(11) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979.**, *44*, 2169 and references cited therein.

(12) The stereochemistry of **9b** is based on empirical rules governing elution orders of diasteromeric carbamates such as **9a** (the 1′*S*,3*R*-diastereomer **9a** eluted after the 1′*S*,3*S*-diastereomer on normal phase silica gel with 10% EtOAc/hexanes as eluent). This stereochemical assignment was confirmed in the following manner. Alcohol **8** was oxidized (Dess–Martin periodinane,[13] CH_2Cl_2, 83% yield) to give the corresponding ketone, which was then reduced (Darvon alcohol-$LiAlH_4$,[14] Et_2O, −78 °C to room temperature) to give primarily **9b** (65% yield, 58% ee). It is well established that the Darvon alcohol-$LiAlH_4$ complex reduces propargyl ketones to primarily *R*-propargyl alcohols.[14]

(13) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(14) (a) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339. (b) Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 582.

(15) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

(16) (a) Boardman, L. D.; Bagheri, V.; Sawada, H.; Negishi, E.-I. *J. Am. Chem. Soc.* **1984**, *106*, 6105. (b) Negishi, E.-I. *Acc. Chem. Res.* **1987**, *20*, 65.

(17) This may be due in part to a ring size effect on the rate of the [1,5]-hydrogen shift which has been previously observed: Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81.

(18) (a) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, *637*. (b) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43.

(19) (a) Paquette, L. A.; Itoh, I.; Lipkowitz, K. B. *J. Org. Chem.* **1976**, *41*, 3524. (b) Mitra, M. N.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1974**, *39*, 2931. (c) Bauld, N. L. *J. Am. Chem. Soc.* **1962**, *84*, 4347.

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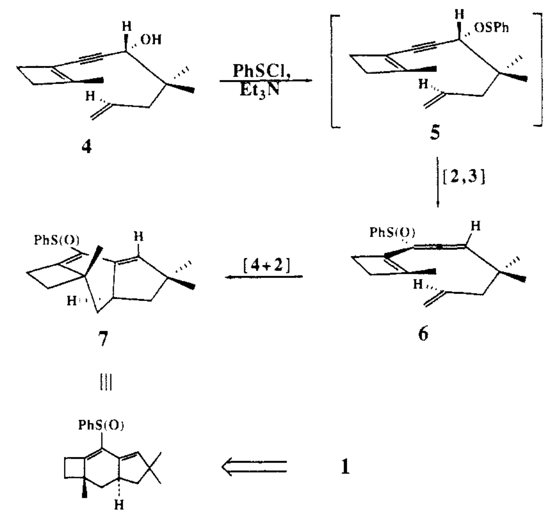
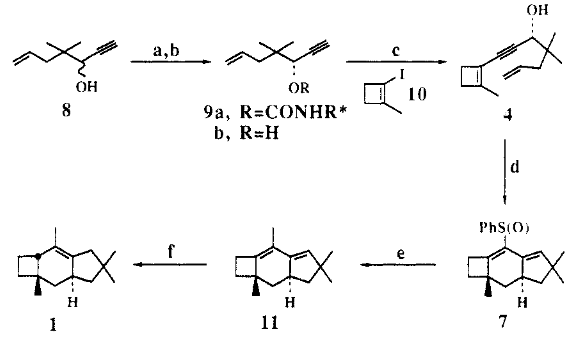
Scheme II



Scheme III



R*=CH(1-Napthyl)CH$_3$

(a) (*S*)-(+)-1-(1-naphthyl)ethyl isocyanate, $Me_2NCH_2CH_2OH$, PhH, reflux, 48 h (81%). (b) $HSiCl_3$, Et_3N, PhH, room temperature, 48 h (76%). (c) **10**, $Pd(PPh_3)_2Cl_2$, CuI, Et_2NH, room temperature, 6 h (77%). (d) PhSCl, Et_3N, CH_2Cl_2, −78 °C, 2 h; room temperature, 38 h (70%). (e) MeMgBr, $Ni(dppp)Cl_2$, THF, reflux, 18 h (62%). (f) Na/NH_3, *t*-BuOH, −78 °C, 3 h (69%).

(+)-sterpurene, identical by high-field ^1H NMR with the natural product. The observed optical rotation, $[\alpha]_D$ +64.9 (*c* 1.54, $CHCl_3$), was identical within experimental error with that of natural sterpurene, $[\alpha]_D$ +65.3 (*c* 0.87, $CHCl_3$),[20] thus demonstrating that the central–axial–central chiral element transfer process, including the intramolecular Diels–Alder reaction, proceeded with complete enantio- and diastereoselectivity and also that the absolute stereochemistry of (+)-sterpurene is that which is shown.[21]

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Supplementary Material Available: Spectral data for selected compounds (3 pages). Ordering information is given on any current masthead page.

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(20) Ayer, W. A., personal communication.

(21) While this work was being carried out, Dr. C. Abell (Cambridge University) informed us that the absolute configuration of 7,12-dihydroxysterpurene is the same as we have determined for sterpurene itself.

Macromolecular Stereochemistry: A Cooperative Deuterium Isotope Effect Leading to a Large Optical Rotation

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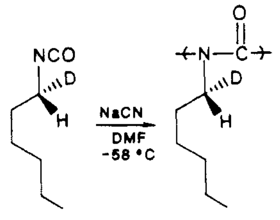
Poly((*R*)-1-deuterio-*n*-hexyl isocyanate) (**1**),[1-3] a macromolecule configurationally chiral only by virtue of deuterium substitution, exhibits a surprisingly high[4] D-line specific rotation of −367° in dilute solution in chloroform at 25 °C.



(1)

The source of the optical activity for **1** can be traced, by inspection of the ultraviolet and circular dichroism spectra exhibited in Figure 1, to electronic absorption bands associated with the recurring amide group backbone structure.[5] This is confirmed by comparison of these spectral characteristics for **1** (Figure 1) with those of poly((*R*)-2,6-dimethylheptyl isocyanate) (**2**)[6] ($[\alpha]^{21}_D$

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(1) Prepared from (*R*)-1-deuterio-*n*-hexyl isocyanate (see ref 2 below) by anionic polymerization following: Shashoua, V. E.; Sweeny, W.; Tietz, R. F. *J. Am. Chem. Soc.* **1960**, *82*, 866.

(2) The precursor (*R*)-1-deuterio-*n*-hexylamine preparation parallels: Streitweiser, A., Jr.; Schaeffer, W. D. *J. Am. Chem. Soc.* **1956**, *78*, 5597. Streitweiser, A., Jr.; Wolfe, J. R. *J. Org. Chem.* **1963**, *28*, 3263. Deuterium coupling in the ^{13}C NMR specified the isotopic site at C-1. The isocyanate was prepared following: Farlow, M. W. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 521.

(3) The Fourier transform infrared spectra of cast films of **1** and poly(*n*-hexyl isocyanate), with the exception of the carbon–deuterium stretching mode at 2221 cm^{-1} were identical from 4000 to 1500 cm^{-1}. Weight average molecular weight of **1**, M_w, determined by low angle light scattering, 870 000; radius of gyration $\langle R_G{}^2\rangle^{1/2}$: 1680 Å in tetrahydrofuran (THF). Intrinsic viscosity of **1** $[\eta]$, uncorrected for shear, 37 dlg^{-1} (THF). Polydispersity estimated by gel permeation chromatography on three Ultrastyragel columns (100 Å, 10^3 Å, 10^5 Å) with a universal calibration curve, $M_w/M_n = 1.27$. See: Yau et al. (Yau, W. W.; Kirkland, J. J.; Bly, D. D. *Modern Size Exclusion Liquid Chromatography*; Wiley-Interscience: New York, 1979) for explanations of these terms.

(4) For early literature in the area of optically active isotopically substituted molecules, see: Loewus, F. A.; Westheimer, F. H.; Vennesland, B. *J. Am. Chem. Soc.* **1953**, *75*, 5018. Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1953**, *75*, 5014. Levy, H. R.; Loewus, F. A.; Vennesland, B. *J. Am. Chem. Soc.* **1957**, *79*, 2949. Althouse, V. E.; Feigl, D. M.; Sanderson, W. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1966**, *88*, 3595. For reviews, see: Arigoni, D.; Eliel, E. L. In *Topics in Stereochemistry*; Wiley: 1969; Vol. 4, p 127ff. Verbit, L. In *Progress in Physical Organic Chemistry*; Wiley-Interscience: 1970; Vol. 7, p 51ff; Barth, G.; Djerassi, C. *Tetrahedron* **1981**, *37*, 4123.

(5) Troxell, T. C.; Scheraga, H. A. *Macromolecules* **1971**, *4*, 528. Milstein, J. B.; Charney, E. *Macromolecules* **1969**, *2*, 678.

(6) The monomeric isocyanate was obtained from the carboxylic acid following Kaiser and Weinstock (Kaiser, C.; Weinstock, J. *Org. Synth.* **1971**, *51*, 48). The acid was prepared via hydrogenation of citronellic acid obtained from (*R*)-(+)-pulegone. See: Lukěs, R.; Zobácŏvá, A.; Plešek, J. *Croat. Chem. Acta* **1957**, *29*, 201. Plešek, J. *Chem. Listy.* **1956**, *50*, 1854. Chan, K. K.; Cohen, N.; DeNoble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497. Elemental analysis for **2** calcd C, 70.96; H, 11.31; N, 8.27. Found: C, 70.99; H, 11.83; N, 8.21. The enantiomeric excess of the starting (*R*)-(+)-pulegone is 92–94% based on the observed optical rotation. See: Valentine, D., Jr.; Chan, K. K.; Scott, C. G.; Johnson, K. K.; Toth, K.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 62. $[\alpha]_D = 8.4°$ (neat, 1 = 1) for the derived (*R*)-(+)-citronellic acid. The intrinsic viscosity and weight average molecular weight of **2** were $[\eta] = 9.5$ dlg^{-1} in $CHCl_3$ and $M_w = 300\,000$ in $CHCl_3$, respectively. Radius of gyration $\langle R_G{}^2\rangle^{1/2}$ in $CHCl_3$ was 540 Å.

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