are assigned to the signals at 125.69, 127.65, and 128.39 ppm, while C(9), the carbon atom attached to a prismane carbon, is assigned to the signal at 137.45 ppm. This is consistent with the carbon attached to the methyl group in toluene (137.4 ppm).[16] The methyl carbons, which are primary and show relatively strong signals, appear in the 0–35 ppm region for methyl carbons of alkanes.[16,17]

Among the six prismane carbons, there are four chemically different carbon atoms, and four signals are observed. Prismane itself exhibits a signal at 30.6 ppm.[1] However, substituent effects shift the signals downfield. The signals at 45.21 and 54.83 ppm are approximately equal and about twice the relative intensity of those at 46.20 and 48.92 ppm. Therefore, the former signals are assigned to the equivalent C(3),C(6) and C(4),C(5) sets, and the latter are assigned to C(1) and C(2).

(16) Silverstein, R. M.; Bassler, G. G.; Morrill, T. C. *Spectroscopic Identification of Organic Compounds*, 4th ed.; Wiley: New York, 1981; Chapter 5.

(17) Abraham, R. J., Loftus, P. *Proton and Carbon-13 NMR Spectroscopy*; Heyden and Sons: London, 1979; p 26.

Acknowledgment. We gratefully acknowlede the U.S. Army Armament Research and Development Command, Dover, NJ, for support of this work.

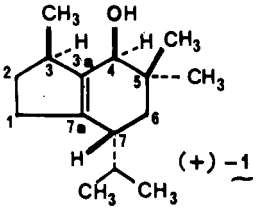
Supplementary Material Available: Details of data collection and structure refinement, atomic positional parameters, thermal parameters, and complete tables of bond lengths and angles (7 pages). Ordering information is given on any current masthead page.

Communications

Expeditious, Stereocontrolled Syntheses of Racemic and Natural Brasilenol through Intramolecular Asymmetry Transfer. Absolute Stereochemistry of Brasilenol

Summary: Brasilenol, a marine metabolite, has been efficiently synthesized in both racemic and natural forms through the use of a highly selective palladium-catalyzed double bond migration.

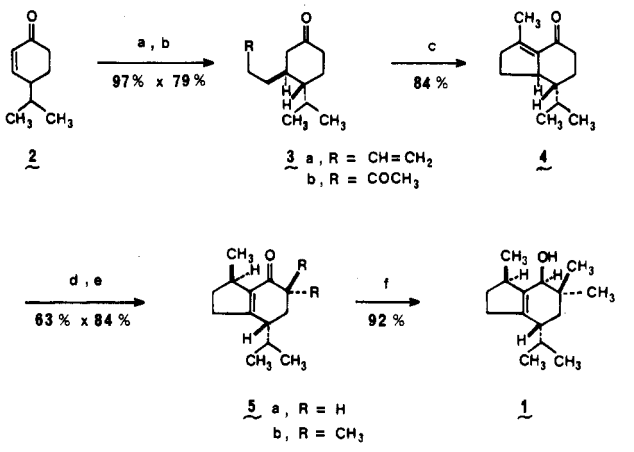
Sir: (+)-Brasilenol (1), a metabolite from the sea hare *Aplysia brasiliana* and the red alga *Laurencia obtusa*, was first isolated in 1978 by Stallard, Fenical, and Kittredge.[1]



(+) – Brasilenol

The novel nonisoprenoid structure and relative stereochemistry that were formulated for this possible feeding deterrent[2] have recently been confirmed by total synthesis.[3] In this paper we report a much more effective approach to racemic brasilenol (7 steps, 31% overall yield vs. 13 steps, 5% overall yield) and the first synthesis of natural brasilenol through an unusual intramolecular transfer of asymmetry. The enantioselective synthesis serves to define for the first time the absolute stereochemistry of (+)-brasilenol and, hence, also that of (+)-4-epibrasilenol and brasilenol acetate (from *Aplysia brasiliana*).[4]

Scheme I[a]



[a] (a) ∿MgBr, CuI, THF; (b) $PdCl_2$, CuCl, O_2, DMF-H_2O; (c) *t*-BuOK, *t*-BuOH; (d) 10% Pd-C, H_2, C_6H_6; (e) $LiN(i\text{-}C_3H_7)_2$, THF, CH_3I (2×); (f) $LiB(C_2H_5)_3H$, THF.

Commercially available racemic cryptone (**2**)[5] underwent smooth, copper-mediated conjugate addition of 3-butenylmagnesium bromide[6] to provide stereoselectively (≥95% trans[7]) in 97% yield ketone **3a**[8] (Scheme I).

(1) (a) Stallard, M. O.; Fenical, W.; Kittredge, J. S. *Tetrahedron* **1978**, *34*, 2077–2081. (b) See also: Fenical, W.; Sleeper, H. L.; Paul, V. J.; Stallard, M. O.; Sun, H. H. *Pure Appl. Chem.* **1979**, *51*, 1865–1874. For an excellent review on the metabolites of marine algae and herbivorous marine molluscs, see: Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251–280.

(2) For a discussion of the chemical defense and evolutionary ecology of opisthobranchs, see: Faulkner, D. J.; Ghiselin, M. T. *Mar. Ecol. Prog. Ser.* **1983**, *13*, 295–301. See also: Stallard, M. O.; Faulkner, D. J. *Comp. Biochem. Physiol.* **1974**, *49B*, 25–35 and ref 1.

(3) Greene, A. E.; Coelho, F.; Barreiro, E. J.; Costa, P. R. R. *J. Org. Chem.* **1986**, *51*, 4250–4253.

(4) (+)-Brasilenol, (+)-4-epibrasilenol, and brasilenol acetate (from *Aplysia brasiliana*) have been shown to belong to the same enantiomeric series.

(5) Racemic cryptone can now be obtained from the Aldrich Chemical Co. Prior to this availability, it was discovered that **2** (essentially racemic) could be conveniently obtained in 85% yield from (+)-nopinone by treatment with 2.0 equiv of aluminum chloride in methylene chloride for 70 min at 0 °C (unpublished results). Cf.: Wallach, O. *Ann.* **1907**, *356*, 227–249; **1908**, *359*, 265–289.

(6) See: Paquette, L. A.; Galemmo, R. A., Jr.; Caille, J.-C.; Valpey, R. S. *J. Org. Chem.* **1986**, *51*, 686–695 and references cited therein.

(7) The stereochemical result of this type of addition is well precedented. See: Posner, G. *Org. React. (N. Y.)* **1972**, *19*, 1–113. Piers, E.; Gavai, A. V. *Tetrahedron Lett.* **1986**, *27*, 313–316. Predictably, the conjugate addition reaction of 3-butenylmagnesium bromide with α′, α′-dimethylcryptone under similar conditions afforded a mixture of cis and trans adducts.

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Wacker oxidation of **3a** was then readily accomplished under Tsuji's conditions[9] to give dione **3b**[8,10] in 79% yield. In contrast to the aldol condensation of related cyclopentanones,[6] aldol cyclization of cyclohexanone **3b** with potassium *tert*-butoxide in *tert*-butyl alcohol afforded only the conjugated product **4**[8] (84% yield).

It was hoped that enone **4** might be made to suffer a palladium-hydrogen-induced migration of the double bond from the Δ^3 to the alternative tetrasubstituted, conjugated position. From previous studies it was known that the entering and leaving hydrogens are generally cofacial in this type of transformation,[11] and *thus a successful* $\Delta^3 \rightarrow \Delta^{3a(7a)}$ *migration was expected to deliver not only the required double bond isomer but also the necessary trans relationship at C-3 and C-7.* In the event, this key conversion proceeded readily to give *exclusively* the trans[12] product **5a**,[8] which under optimal conditions could be isolated in up to 63% yield. This means of transferring the relative stereochemistry generated through conjugate addition to the allylic (or other) substituents in cyclized products should be of general value.

The completion of the synthesis could be easily achieved. Hydrindenone **5a** was dimethylated with lithium diisopropylamide and methyl iodide in tetrahydrofuran to produce in 84% yield brasilenone,[8] which for steric reasons on reduction with lithium triethylborohydride afforded only racemic brasilenol,[8] mp 63-64 °C, in 92% yield. Spectral comparison of this material with the natural substance established unambiguously its identity.

Application of the same efficient sequence of reactions to (*R*)-(−)-cryptone,[13] secured from 4-isopropylcyclohexanone by using Koga's elegant enantioselective deprotonation-oxidation procedure,[14] readily produced optically pure (+)-brasilenol.[8] Thus, (+)-brasilenol has the absolute stereochemistry 3*R*,4*S*,7*R*.[4]

In summary, a concise, highly stereocontrolled route to brasilenol from cryptone has been developed based on a novel asymmetry transfer reaction. The synthesis establishes for the first time the absolute stereochemistry of the marine natural product as well as that of two congeneric metabolites.

Acknowledgment. Dr. J. L. Luche is thanked for his interest in this work and V. J. Paul for having supplied the spectra of brasilenone and brasilenol. Financial support from the CNRS (France) and the CNPq (Brazil) and fellowship awards from the CNPq to A.A.S. and P.R.R.C. are gratefully acknowledged.

Supplementary Material Available: Experimental procedures for compounds 1 and **3-5** (4 pages). Ordering information is given on any current masthead page.

(8) **2** → **3a**: To 8.27 g of CuI in 19 mL of THF at −20 °C was added 3-butenylmagnesium bromide in THF (from 8.9 mL of 4-bromo-1-butene and 2.11 g of Mg in 180 mL of THF). After 30 min, 3.00 g of **2** in 54 mL of THF was added and the mixture was stirred at 0 °C (2 h) and then processed as usual to give **3a** (4.10 g, 97%): IR (film) 3060, 1715, 1638, 995, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.78 (m, 1 H), 5.00 (m, 2 H), 0.99 (d, J = 6.5 Hz, 3 H), 0.82 (d, J = 6.5 Hz, 3 H); mass spectrum, m/e 195 ($M^+ + 1$). Anal. ($C_{13}H_{22}O$) C, H. (+)-**3a** (ca. 65% ee): $[\alpha]^{26}_D$ +22° (c 4.6, $CHCl_3$). **3a** → **3b**: Under O_2, 401 mg of $PdCl_2$ and 6.76 g of CuCl in 68 mL of DMF-H_2O (7:1) were stirred 2 h and then treated with 2.20 g of **3a** in 23 mL of THF. After 3 h, normal isolation gave **3b** (1.87 g, 79%): IR (film) 1710, 1360, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.84 (d, J = 6.8 Hz, 3 H); mass spectrum, m/e 211 ($M^+ + 1$). Anal. ($C_{13}H_{22}O_2$) C, H. (+)-**3b** (ca. 65% ee): $[\alpha]^{26}_D$ + 24° (c 4.6, $CHCl_3$). **3b** → **4**: Dione **3b** (105 mg) was stirred with 160 mg of *t*-BuOK in 10 mL of *t*-BuOH for 15 min to give after processing **4** (81 mg, 84%). **4**: IR (film) 1680, 1620, 1260, 1195, 930 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.75 (m, 1 H), 2.08 (m, 3 H), 0.97 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.9 Hz, 3 H); mass spectrum, m/e 193 ($M^+ + 1$). Anal. ($C_{13}H_{20}O$) C, H. (+)-**4** (ca. 65% ee): $[\alpha]^{26}_D$ +21° (c 5.1, $CHCl_3$). **4** → **5a**: Enone **4** (100 mg) was slowly stirred for 2.5 h with 50 mg of 10% Pd-C in 4 mL of benzene at 60 °C under H_2 to give after purification **5a**[3] (63 mg, 63%). **5a**: IR (film) 1660, 1615, 1380, 1200 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 3.15 (m, 1 H), 1.26 (d, J = 6.9 Hz, 3 H), 0.72 (d, J = 6.8 Hz, 3 H), 0.54 (d, J = 6.8 Hz, 3 H); mass spectrum, m/e 192 (M^+). (+)-**5a** (two recrystallizations from pentane): mp 45-46 °C; $[\alpha]^{21}_D$ + 21.6° (c 1.7, $CHCl_3$). **5a** → **5b**:[3] 84% yield. (+)-**5b**: $[\alpha]^{21}_D$ +44.2° (c 0.6, $CHCl_3$) [lit.[1a] $[\alpha]^{21}_D$ +40.9° (c 0.95, $CHCl_3$)]. **5b** → **1**:[3] 92% yield. (+)-**1**: mp 55-56 °C (lit.[1a] mp 55-56 °C); $[\alpha]^{21}_D$ +44.0° (c 1.2, $CHCl_3$) [lit.[1a] $[\alpha]^{21}_D$ +33.4° (c 1.58, $CHCl_3$)].

(9) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, 2975-2976. Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth.* **1984**, *62*, 9-13.

(10) This product was also obtained, but less satisfactorily, by conjugate addition of [3,3-(ethylenedioxy)butyl]magnesium iodide followed by acid hydrolysis.[6]

(11) Rylander, P. N. *Catalytic Hydrogenation in Organic Syntheses*; Academic: New York, 1979; pp 36-38, 290. Dana, G.; Weisbuch, F.; Drancourt, J. M. *Tetrahedron.* **1985**, *41*, 1233-1239.

(12) The complete absence of the corresponding cis isomer was confirmed through comparison (TLC, NMR) with an authentic cis sample. It should be noted that there is little difference in energy between the cis and trans isomers (ca. 1:1 after rhodium chloride catalyzed equilibration).[3]

(13) See: Klyne, W.; Buckingham, J. *Atlas of Stereochemistry*; Chapman and Hall: London, 1974; p 78.

(14) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543-545. (*R*)-(+)-*N*-Isopropyl-*N*-(1-phenylethyl)amine was employed and gave (*R*)-(−)-cryptone with an enantiomeric excess of ca. 65%. [See: Galloway, A. S.; Dewar, J.; Reed, J. *J. Chem. Soc.* **1936**, 1595-1597. (−)-Cryptone can also be obtained by resolution (Soffer, M. D.; Gunay, G. E. *Tetrahedron Lett.* **1965**, 1355-1358) and from *Eucalyptus* oils (Cahn, R. S.; Penfold, A. R.; Simonsen, J. L. *J. Chem. Soc.* **1931**, 1366-1369).] Two recrystallizations of (+)-**5a** from pentane efficiently provided optically pure material [^1H NMR with Eu(hfc)$_3$] for the completion of the synthesis.

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A Versatile Protocol for the Stereocontrolled Elaboration of Vicinal Secondary and Tertiary Centers of Relevance to Natural Product Synthesis

Summary: Chiral butenolides derived from L-glutamic acid, D-ribonolactone, or D-mannitol are versatile templates from the stereocontrolled introduction of functional groups. Vicinal and/or alternating patterns of secondary and tertiary substitution can be attained with a high degree of prediction.

Sir: Especially challenging to the synthetic chemist are those structures which possess sequences of consecutive, highly functionalized carbon atoms, a situation frequently encountered in many natural products.[1] Despite dramatic developments in acyclic stereoselection, most notably via

(1) See, for example: Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. Wierenga, W. In *The Total Synthesis of Natural Products*; ApSimon, J. A., Ed.; Wiley-Interscience: New York, 1981; Vol. 4, p 263.

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