tivation energies could not be obtained under acidic or basic conditions for the amide or acidic conditions for the urea due to decomposition at elevated temperatures.

Discussion

It can be reasoned that the difference in acid-catalyzed rate constants for $NH(CH_3)$ and $NH(CH_2)$ is due to differences in the inductive[10a] nature of methyl and benzyl substituents and to differences in their steric bulk.[10b] Under basic conditions the NH(benzyl) was expected to exhibit faster exchange than NH(methyl) due to the enhanced electronegativity of the benzyl group decreasing the availability of the lone-pair electrons on nitrogen by induction. The observed identical base-catalyzed protolysis rate constants for the two NH groups must therefore be due to factors other than polar influences. The greater steric bulk of the benzyl group compared to methyl can account for the observed base-catalyzed rate constants. The expected inductive enhancement of protolysis by the greater electronegativity of the benzyl group is offset by its larger bulk which sterically retards base removal of the proton from the adjacent urea nitrogen.

Under acid-catalyzed conditions, however, the greater electron-withdrawing and greater steric effects of the benzyl group will act in concert to reduce the proton exchange rate of the NH(benzyl) compared to the NH(methyl). The inductive electron-withdrawing effect of the benzyl compared to the methyl reduces availability of the lone-pair electrons, thus decreasing the proportion of protonated NH(benzyl) species (eq 1), a proposal

$$PhCH_2NHCNHCH_3 \overset{H_3O^+}{\rightleftharpoons} PhCH_2\overset{H}{\overset{|}{N}}CNHCH_3 \qquad (1)$$

similar to that postulated for exchange in amide[11] and carbamates.[9] A similar protonated species was proposed for urea.[8] In addition to inductive effects, greater steric hinderance to NH(benzyl) protonation also reduces the amount of protonated NH(benzyl) compared to $NH(CH_3)$.

From the acid-catalyzed rate constants (k_{H^+}) it is clear the two urea NH groups are more basic than the amide NH. Further evidence of this fact can be seen when under basic conditions the amide NH exchanges faster than either of the urea NH's when measured at the same pH.

A quantitative assessment of steric and polar influences on the NH proton exchange kinetics in the title compound cannot be made from this study. It is clear qualitatively, however, that steric and polar influences on NH proton exchange do occur and that they affect the kinetics in a predictable manner.

Acknowledgment. The authors wish to thank the Office of General Research and the School of Pharmacy of the University of Georgia for partial support of this research.

(10) (a) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, Chapter 4, p 87; Taft polar substituent constants (σ^*) are referred to where, compared to methyl, benzyl has a value of +0.22; (b) see ref 10a, Chapter 12, p 287; steric substituent constants (E_s) show that, compared to methyl, benzyl has a value of −0.38.

(11) A. Berger, A. Loewenstein, and S. Meiboom, *J. Amer. Chem. Soc.*, **81**, 62 (1959).

Stereoselective Total Synthesis of (±)-Seychellene

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Abstract: An efficient, highly stereoselective total synthesis of the racemic form of the tricyclic sesquiterpene seychellene (**1**) is described. Conversion of the well-known Wieland–Miescher ketone **8** into the keto tosylate **6** was accomplished in **15** steps. Base-promoted intramolecular alkylation of **6** afforded, in high yield, the tricyclic ketone (±)-norseychellanone (**4**), which was readily converted into (±)-seychellene.

The structurally novel sesquiterpene (−)-seychellene (**1**) is a minor component of commercial patchouli oil, which is derived from *Pogostemon patchouli* Pallet *var. suavis* Hook. The isolation of this natural product was first reported in 1967 by Hirose, *et al.*,[2] while the structural and stereochemical elucidation was elegantly accomplished by Wolff and Ourisson.[3] Structurally and biogenetically, (−)-seychellene (**1**) is obviously closely related to the well-known sesquiterpenoid patchouli alcohol (**2**),[4] with which it cooccurs. We report in this paper[5] a total synthesis of (±)-**1** *via* a highly stereoselective route which fully corroborates the structural and stereochemical assignments.[3]

A careful analysis of the structure of seychellene (**1**) reveals a number of possible "key" reactions which might be employed in the construction of the required tricyclic carbon skeleton. One possibility which we considered, for example, was the intramolecular alkylation of an intermediate such as the bicyclic ketone **3**. This reaction, if successful, would produce (±)-norsey-

(1) Fellow of the Alfred P. Sloan Foundation, 1970–1972.

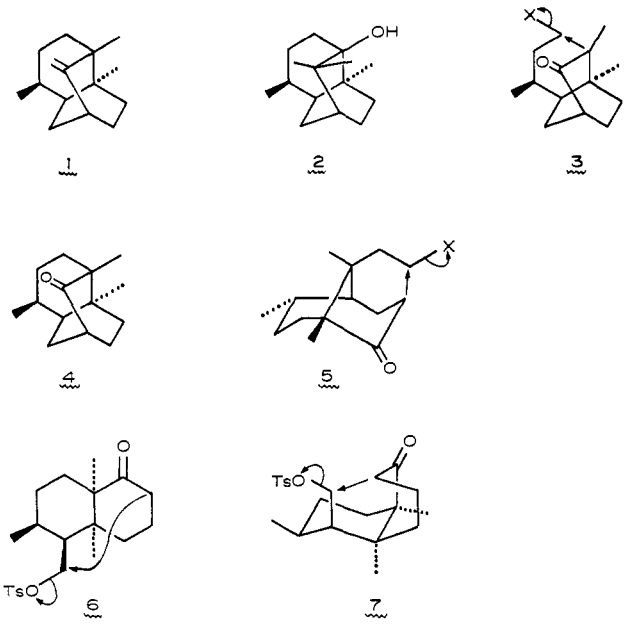
(2) N. Tsubuki, K. Nishimura, and Y. Hirose, *Bull. Chem. Soc. Jap.*, **40**, 597 (1967).

(3) G. Wolff and G. Ourisson, *Tetrahedron Lett.*, 3849 (1968); *Tetrahedron*, **25**, 4903 (1969).

(4) *Cf.* G. Buchi, W. D. MacLeod, Jr., and J. Padilla O., *J. Amer. Chem. Soc.*, **86**, 4438 (1964).

(5) For a preliminary communication regarding part of this work, *cf.* E. Piers, R. W. Britton, and W. de Waal, *Chem. Commun.*, 1069 (1969).

chellanone (**4**). Indeed, a total synthesis of racemic seychellene based upon the intermediacy of **3** has very recently been reported.[6] However, we rejected this approach because of the difficulty associated with the stereoselective construction of the "nonrigid" 4-carbon side chain in **3**. In fact, in the above-mentioned synthesis[6] of (±)-**1**, this difficulty was experienced and it was necessary at one stage in the synthetic sequence to separate a pair of epimeric compounds.

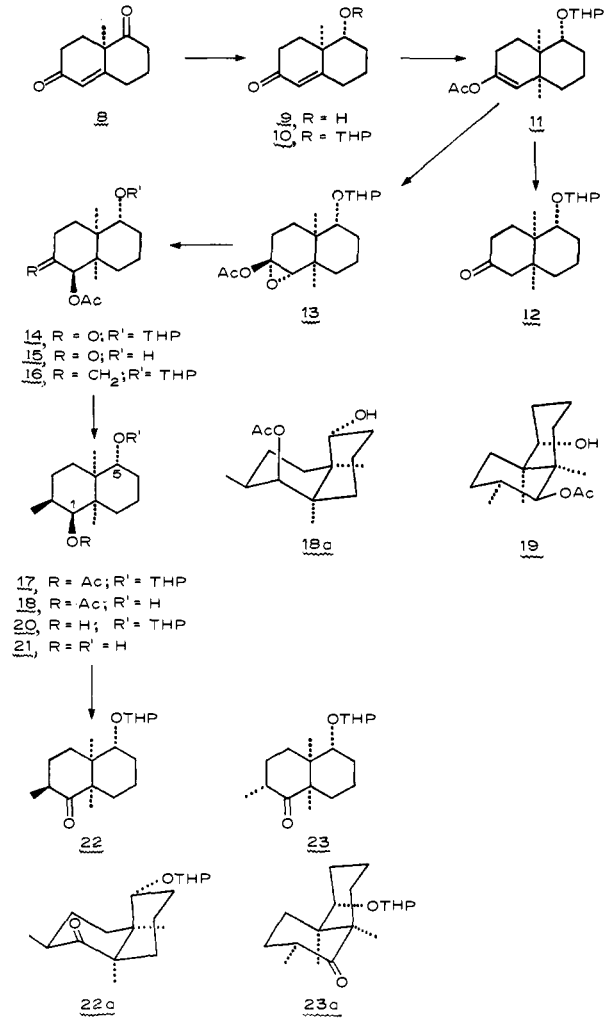


The successful intramolecular cyclization of the substituted bicyclo[3.3.1]nonanone (**5**) would also afford (±)-norseychellanone (**4**). Although this remains as an attractive potential "key" reaction for the synthesis of (±)-**1**, its possible use was rejected because of the obvious difficulties attending the stereochemically unambiguous preparation of the bicyclic intermediate **5**.

The approach which was finally adopted for the synthesis of (±)-seychellene (**1**) involved the intermediacy of the substituted decalone **6**, a compound which appeared to be accessible by stereoselective synthesis from readily available starting materials. Furthermore, molecular models clearly indicated that, in an appropriate conformation (*cf.* **7**), the desired intramolecular alkylation of **6** should be a very facile process. Again, the product of such a reaction would be (±)-norseychellanone (**4**).

The starting material chosen for the synthesis of intermediate **6** was the well-known and readily available Wieland–Miescher ketone **8**[7,8] (see Scheme I). This

Scheme I. Conversion of Wieland–Miescher Ketone **8** Into Decalone **22**



compound not only contained the desired keto group in the B ring, but also possessed the necessary functionality in the A ring (α,β-unsaturated ketone) for the introduction of the methyl groups and the $-CH_2OTs$ moiety (*cf.* **6**).

Before carrying out the necessary elaboration of the A ring of compound **8**, it was necessary to protect the saturated carbonyl group in ring B. Although Corey, *et al.*,[9] had shown that this carbonyl group could be selectively converted into the corresponding ethylene ketal, it was felt that this protecting group would make the stereochemical assignment of a later (proposed) synthetic intermediate very difficult (*vide infra*). Therefore, the saturated carbonyl group of **8** was reduced selectively with sodium borohydride[17] and the resulting keto alcohol **9** was converted in the usual manner into the corresponding tetrahydropyranyl (THP) ether **10**.[18,19]

(6) K. J. Schmalzl and R. N. Mirrington, *Tetrahedron Lett.*, 3219 (1970).

(7) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **33**, 2215 (1950); S. Ramachandran and M. S. Newman, *Org. Syn.*, 41, 38 (1961).

(8) It is interesting to note that the Wieland–Miescher ketone has served as the starting material for total synthesis of a number of other sesquiterpenoids: (+)-longifolene,[9] (±)-copaene,[10] (±)-ylangene,[10] (±)-lindestrene,[11] (±)-sativene,[12] (±)-bulnesol,[13,14] (±)-kessane,[15] and (±)-copacamphene.[16]

(9) E. J. Corey, M. Ohno, P. A. Vatakencherry, and R. B. Mitra, *J. Amer. Chem. Soc.*, 83, 1251 (1961); E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *ibid.*, **86**, 478 (1964).

(10) C. H. Heathcock, *ibid.*, **88**, 4110 (1966); C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *ibid.*, **89**, 4133 (1967).

(11) H. Minato and T. Nagasaki, *Chem. Commun.*, 347 (1967); *J. Chem. Soc. C*, 621 (1968).

(12) J. E. McMurry, *J. Amer. Chem. Soc.*, **90**, 6821 (1968).

(13) M. Kato, H. Kosugi, and A. Yoshikoshi, *Chem. Commun.*, 185 (1970).

(14) C. H. Heathcock, Abstracts of Papers, CIC–ACS Joint Conference, Toronto, Canada, May 24–29, 1970, Organic Abstract No. 16.

(15) M. Kato, H. Kosugi, and A. Yoshikoshi, *Chem. Commun.*, 934 (1970).

(16) J. E. McMurry, *Tetrahedron Lett.*, 3731 (1970).

(17) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2680 (1960).

(18) T. A. Spencer, T. D. Weaver, R. M. Villarica, F. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).

(19) It should be noted that the THP protecting group possesses a center of asymmetry and, since it cannot be introduced stereoselectively, compound 10 exists as a mixture of two epimers. This probably accounts for the fairly large range in the melting point of **10** (see Experi-

The introduction of the second angular methyl group into compound **10** was accomplished by reaction of the latter with lithium dimethylcuprate.[20,21] It is now well established that this reagent adds very stereoselectively to $\Delta^{1,9}$-octal-2-ones to produce as the sole conjugate addition products the corresponding cis-fused decalone systems.[22,23] Furthermore, since the conjugate addition to a compound such as **10** generates a specific enolate anion, it is possible to trap this latter species with electrophilic reagents such as acetyl chloride.[24] Since we felt that the resulting enol acetate **11** would be of greater synthetic utility than the corresponding ketone **12**, this procedure was adopted.

After performing the lithium dimethylcuprate addition to compound **10** under a wide variety of conditions, it was found that low concentrations of organocopper reagent and low reaction temperatures (−25°), followed by rapid quenching of the reaction mixture with excess acetyl chloride, gave the best results. In order to ensure basic work-up conditions, the quenched solution was immediately poured into a rapidly stirred ice–ammonium hydroxide mixture. After isolation and purification, the enol acetate **11** was obtained in 88% yield.

It is interesting to note here that the decalone **12** is also best prepared from **10** *via* the enol acetate **11**. Thus, reaction of **10** with lithium dimethylcuprate in the manner described above, followed by quenching of the reaction mixture with aqueous ammonium chloride[20] or with dilute hydrochloric acid,[22] afforded the decalone **12** in only 50% yield. Analysis of the product seemed to indicate that during the quenching procedure some 1,2 addition to the saturated carbonyl of **12** had taken place.[20,22] Furthermore, partial removal of the THP protecting group had also occurred. Alternatively, when the enol acetate **11** was subjected to base hydrolysis (potassium carbonate in methanol–water), the decalone **12** was obtained in 80% yield and the conversion of **10** into **12** *via* the enol acetate **11** was thus much more convenient and efficient than the more direct conversion employing acid quenching.

Epoxidation of the enol acetate **11** with *m*-chloroperbenzoic acid in dry benzene afforded the epoxy acetate **13**. The stereochemical assignment was based upon the well-known fact that cis decalin systems are preferentially attacked from the less-hindered, convex face of the molecule.[10,12] Since the epoxy acetate **13** was unstable to column chromatography and to the fairly high temperatures necessary for distillation, the crude material was immediately subjected to thermal rearrangement[25] to the corresponding acetoxy ketone **14**. It has been shown[26] that the thermal rearrangement of epoxy acetates such as **13** involves intramolecular acetate migration with inversion of configuration. Therefore, on this basis, the stereochemistry of the resulting product must be as shown in structure **14**. Removal of the THP protecting group from **14** by mild hydrolysis produced a sharp melting solid, the spectral data of which were in complete accord with structure **15**.

Reaction of the acetoxy ketone **14** with 3 equiv of methylenetriphenylphosphorane in dimethyl sulfoxide[27] at 50° for 2.5 hr resulted in selective reaction with the ketone carbonyl group. When more vigorous reaction conditions were employed (higher temperatures, longer reaction times, and/or greater amounts of phosphorane) partial or complete removal of the acetyl group also took place, presumably by attack of the Wittig reagent on the acetate carbonyl. However, under these conditions, the yield of reaction product also significantly decreased, while the milder, more selective conditions produced the acetoxy olefin **16** in 73% yield.

Since attempted hydrogenation of olefin **16** employing conventional catalysts would probably have resulted in at least partial hydrogenolysis of the allylic acetate,[28] the homogeneous catalyst tris(triphenylphosphine)chlororhodium[29] was chosen for the hydrogenation. In addition to alleviating the problem of hydrogenolysis, this catalyst has the added advantage of normally reducing olefinic double bonds in a highly stereoselective manner.[29] Indeed, hydrogenation of **16** with the complex rhodium catalyst produced, in 90% yield, only one product, the desired acetate **17**. On the basis of steric approach control, we fully expected the hydrogenation product to possess the stereochemistry shown in structure **17** and, indeed, the fact that the secondary methyl group of this compound was in the β configuration was subsequently established unambiguously (*vide infra*). At this stage, however, it is pertinent to point out that the proton magnetic resonance (pmr) spectrum of the acetate alcohol **18**, obtained by removal of the THP protecting group from **17**, fully supported the stereochemical assignment. Thus, the signal due to the proton adjacent to the acetoxy group appeared as a clean doublet (J = 2.5 Hz) at τ 5.08, while the proton adjacent to the hydroxyl group produced a broad multiplet (width at half-height $\simeq$ 19 Hz) at τ 5.70. On the basis of conformational analysis, it can readily be seen that the favored chair–chair conformation of compound **18** should be as shown in **18a**. The observed coupling of the two signals mentioned above is in excellent agreement with conformation **18a**, since one would expect a relatively small (1–7 Hz) equatorial–axial coupling for the –C*H*OAc proton, and a large combined axial–axial (8–14 Hz) and axial–equatorial coupling for the –C*H*OH proton. On the other hand, the more stable

mental Section) and of some of the subsequent synthetic intermediates containing the THP functionality. Also, since the isomer ratio may vary with the method and solvent of recrystallization, the melting points of compounds possessing the THP protecting group are not always reproducible. Finally, complex proton magnetic resonance spectra may result when the signals for one isomer do not coincide with those of the other. For the sake of simplicity, mixtures of isomers resulting from the asymmetry of the THP group will be referred to as one compound. Whenever possible, the THP functionality was removed, and the compound was characterized as the free parent alcohol.

(20) H. O. House, W. L. Respess, and G. M. Whitesides, *ibid.*, 31, 3128 (1966).

(21) H. O. House and W. F. Fischer, Jr., *ibid.*, 33, 949 (1968).

(22) E. Piers and R. J. Keziere, *Tetrahedron Lett.*, 583 (1968); *Can. J. Chem.*, 47, 137 (1969).

(23) J. A. Marshall and H. Roebke, *J. Org. Chem.*, 33, 840 (1968).

(24) *Cf.* J. A. Marshall and A. R. Hochstetler, *J. Amer. Chem. Soc.*, 91, 648 (1969).

(25) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, 26, 4563 (1961); *J. Amer. Chem. Soc.*, 83, 4623 (1961).

(26) K. L. Williamson, J. I. Coburn, and M. F. Herr, *J. Org. Chem.*, 32, 3934 (1967).

(27) R. Greenwald, M. Chaykovsky, and E. J. Corey, *ibid.*, 28, 1128 (1963).

(28) M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).

(29) F. H. Jardine and G. Wilkinson, *ibid.*, *C*, 270 (1967); A. J. Birch and K. A. M. Walker, *Tetrahedron Lett.*, 1935 (1967); C. Djerassi and J. Gutzwiller, *J. Amer. Chem. Soc.*, 88, 4537 (1966); E. Piers and K. F. Cheng, *Can. J. Chem.*, 46, 377 (1968); E. Piers and K. F. Cheng, *ibid.*, 48, 2234 (1970).

chair–chair conformation of the alternative hydrogenation product (*cf.* **19**) would not be expected to exhibit the observed coupling constants.

Base hydrolysis of the acetate **17** afforded the crystalline monoalcohol **20** in 84% yield. Removal of the THP functionality from **20** produced the diol **21**, a highly crystalline compound with a very sharp melting point. Again the pmr spectrum of this material fully supported the structural and stereochemical assignment. In particular, the C-1 proton exhibited a doublet (J = 3 Hz) at τ 6.68, while the C-5 proton appeared as a pair of doublets at τ 5.63, due to the X part of an ABX system with J_{AX} = 11 Hz and J_{BX} = 5 Hz.

In order to preserve the THP protecting group, oxidation of the alcohol **20** was accomplished with chromium trioxide in pyridine,[30] affording a 77% yield of the corresponding ketone **22**. The latter was recovered *unchanged* from refluxing methanolic sodium methoxide and upon reduction with lithium aluminum hydride in ether, followed by acid-catalyzed removal of the THP protecting group, afforded, in very high yield, a diol which was shown to be identical (melting point, mixture melting point, ir spectrum) with diol **21**.

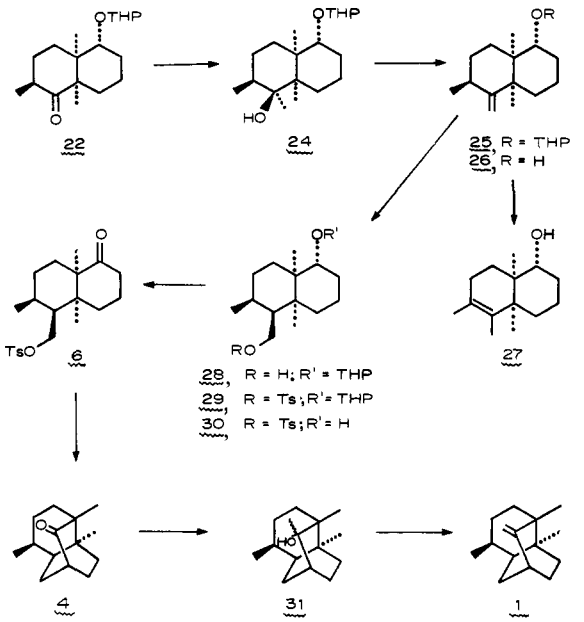
The stereochemistry of the ketone **22** requires brief comment. Obviously, the secondary center adjacent to the carbonyl in this compound is epimerizable and therefore, unless one of the two possible epimers **22** or **23** is considerably more stable than the other, one might expect a mixture at this point in the synthesis. However, on the basis of conformational analysis, it can readily be seen that the favored chair–chair conformation of **22** (*cf.* **22a**) is indeed appreciably more stable than favored chair–chair conformation of **23** (*cf.* **23a**). This is mainly due to the presence of a 1,3-diaxial interaction (CH_3–OTHP) in the latter compound, while there are no similar interactions present in compound **22**. It can now also be clearly seen why the saturated carbonyl group of the Wieland–Miescher ketone was initially protected *via* the THP derivative of the corresponding alcohol. The presence of this α-orientated oxygen substituent ensured that, at equilibrium, compound **22** (with desired stereochemistry) was clearly favored over the epimeric ketone **23**.

As already mentioned, lithium aluminum hydride reduction of **22** afforded, after removal of the THP protecting group from the reduction product, the diol **21**. Since the hydride reagent would be expected to approach the carbonyl from the less hindered, convex side of the molecule,[10,12] this observation provided excellent evidence for the fact that the stereochemistry assigned to our previous synthetic intermediates was indeed correct.

Having successfully obtained the ketone **22**, it was now necessary to attempt the elaboration of this compound to the key keto tosylate intermediate **6** (see Scheme II). Reaction of **22** with methylenetriphenylphosphorane in dimethyl sulfoxide[27] proved to be very sluggish and produced the corresponding exocyclic olefin in only poor yield. Presumably this is due to the fact that the carbonyl group in **22** is in a sterically crowded environment. However, successive treatments of the ketone **22** with methyllithium in ether afforded, in 70% yield, the corresponding tertiary

(30) G. I. Poos, G. E. Arth, R. E. Bayler, and L. H. Sarett, *J. Amer. Chem. Soc.*, 75, 422 (1953).

Scheme II. Conversion of Decalone **22** into (±)-Seychellene (**1**)



alcohol **24**. Dehydration of the latter with thionyl chloride in benzene–pyridine afforded a quantitative yield of crude product. That the major component of this crude material was the desired exocyclic olefin **25** was clear from the following observations. (a) The crude olefinic material was converted into the tosylate **29** in 73% overall yield (*vide infra*). (b) The ir spectrum exhibited strong absorptions at 6.15 and 11.13 μ, clearly indicating the presence of a terminal olefinic functionality. (c) Although the pmr spectrum of the crude olefin was too complex for complete analysis, presumably due to the asymmetry present in the THP group,[19] there were no substantial signals in the vinyl methyl region (τ 8–8.5), and the amount of isomeric olefin containing an endocyclic double bond was, therefore, quite small.

In order to more fully characterize the olefin **25**, removal of the THP protecting group was attempted. However, when **25** was treated under even very mildly acidic conditions, removal of the THP group was accompanied by partial isomerization of the terminal olefinic double bond into the more substituted endo position. Attempted purification of **25** by preparative glc on two different columns also caused partial isomerization of the carbon–carbon double bond, with the ratio of the two olefinic isomers (**26** and **27**) somewhat dependent upon the glc column used and upon the conditions employed. Moreover, the glc conditions also caused removal of the THP protecting group. However, in order to demonstrate that during the dehydration of **24** no skeletal rearrangement had taken place, analytical samples of the isomeric olefins **26** and **27** were collected by preparative glc. The ir and pmr spectra of these two compounds were in complete accord with the assigned structures.

Subjection of olefin **25** to hydroboration in tetrahydrofuran,[31] followed by decomposition of the intermediate alkylborane by treatment of the reaction mixture with alkaline hydrogen peroxide, gave the crude alcohol **28**. Again, the attack of borane on the double bond of **25** was expected to take place from the less

(31) *Cf.* G. Zweifel and H. C. Brown, *Org. React.*, 13, 1 (1963).

hindered, convex side of the molecule[10,12] to yield the primary alcohol **28**, with desired stereochemistry.

The crude alcohol **28**, upon reaction with *p*-toluenesulfonyl chloride in pyridine, afforded the crystalline tosylate **29**, in 73% overall yield from the olefin **25**. Removal of the THP protecting group from **29** by treatment of the latter with *p*-toluenesulfonic acid in methanol afforded the crystalline alcohol **30** in 77% yield. The sharp melting point and the spectral data indicated that this material was homogeneous. Treatment of **30** with chromium trioxide in pyridine[30] at room temperature effected oxidation of the secondary alcohol without destruction or loss of the tosylate functionality. The product, keto tosylate **6**, was obtained in 94% yield and exhibited spectral data in complete accord with the assigned structure.

Having thus obtained the keto tosylate **6**, with the required stereochemistry at all four asymmetric centers, the crucial (proposed) intramolecular cyclization of **6** to (±)-norseychellanone (**4**) could now be tested. This was, in fact, found to be an extremely facile process. Thus, treatment of the keto tosylate **6** with methylsulfinyl carbanion[32] in dimethyl sulfoxide at 75° for 2 hr gave, in 90% yield, (±)-norseychellanone (**4**). Analysis by glc showed that the product consisted of only one component.

Since Wolff and Ourisson[3] had observed that the carbonyl group of norseychellanone (**4**), prepared from (−)-seychellene (**1**), was very unreactive, the conversion of this ketone into the natural product using methylenetriphenylphosphorane was not attempted. However, treatment of (±)-noreseychellanone (**4**) with excess methyllithium in refluxing ether for 2 days afforded the corresponding tertiary alcohol **31** in quantitative yield. Dehydration of the latter with thionyl chloride in benzene–pyridine gave a quantitative yield of (±)-seychellene (**1**). An analytical sample of the latter was obtained by preparative glc, and exhibited spectral data (ir, pmr) and glc retention times identical with those of authentic (−)-seychellene (**1**).[33] Thus, the stereoselective synthesis described above fully supports the structural and stereochemical assignments made by Wolff and Ourisson.[3]

Experimental Section

General. Melting points and boiling points are uncorrected. Uv spectra were measured in methanol solution on either a Cary, Model 14, or a Unicam, Model SP-800, spectrophotometer. Routine ir spectra were recorded on a Perkin-Elmer Infracord Model 137 spectrophotometer, while all comparison spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer. Pmr spectra were taken in deuteriochloroform solution on Varian Associates spectrometers, Model A-60, T-60, and/or HA-100. Signal positions are given in the Tiers τ scale, with tetramethylsilane as an internal standard; the multiplicity, integrated peak areas, and proton assignments are indicated in parentheses. High-resolution molecular weight determinations were measured on an AEI, type MS9, mass spectrometer. Glc was carried out on an Aerograph Autoprep, Model 700. The following columns (10 ft × 1/4 in., unless otherwise stated) were employed, with the inert, supporting material being 60–80 mesh Chromosorb W in each case: column A, 10% Apiezon J; column B, 20% Apiezon J; column C (10 ft × 3/8 in.), 30% Apiezon J; column D (10 ft × 3/8 in.), 30% SE-30; column E, 20% SE-30. The specific column used, along with the column temperature and carrier gas (helium) flow rate (in milliliters/minute), are indicated in parentheses. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

Preparation of Keto Alcohol 9. A solution of 3.24 g (0.0858 mol) of sodium borohydride in 375 ml of 100% ethanol was added over 1 hr to a stirred solution of 51.8 g (0.290 mol) of Wieland–Miescher ketone **8** in 750 ml of 100% ethanol at 0°. After the reaction had been allowed to continue for an additional 15 min, 20 ml of glacial acetic acid was added. The solvent was removed under reduced pressure and the residual material was diluted with chloroform. The organic solution was washed twice with water, dried over anhydrous magnesium sulfate, and concentrated. Vacuum distillation of the residual oil afforded 46.5 g (89%) of keto alcohol **9**: bp 150–153° (0.1 mm) [lit.[17] bp 140° (0.25 mm)]; uv (max) 240 mμ (ϵ 13,500); ir (film) 3.00, 6.05, 6.21 μ; pmr τ 4.12 (broad s, 1, olefinic H), 6.45 (m, 1, -C*H*OH), 8.63 (s, 3, tertiary CH_3).

Preparation of Tetrahydropyranyl Ether 10. Anhydrous hydrogen chloride was bubbled into a solution of keto alcohol **9** (174 g, 0.66 mol) and dihydropyran (123 g, 1.47 mol) in methylene chloride (560 ml) until the mixture was warm. After the resulting solution had been allowed to stand for 3 hr at room temperature it was diluted with 400 ml of methylene chloride and then washed with saturated sodium bicarbonate solution and with saturated brine. The solution was dried over anhydrous magnesium sulfate and concentrated. Crystallization of the residue from hexane–ether afforded 240 g (94%) of the tetrahydropyranyl ether **10**: mp 40–45° [lit.[18] mp 55–60°] (for an explanation of this discrepancy see ref 19); uv max 239 mμ (ϵ 13,900); ir ($CHCl_3$) 6.02, 6.20 μ; pmr τ 4.24 (broad s, 1, olefinic H), 5.36 (m, 1, -OC*H*O-), 8.80 (s, 3, tertiary CH_3).

Preparation of Enol Acetate 11. To a stirred suspension of cuprous iodide (68.7 g, 0.36 mol) in dry ether (1250 ml) under a nitrogen atmosphere and at −25° (Dry Ice–carbon tetrachloride slush bath) was added 305 ml of 3.25 *M* methyllithium in ether. A small amount of cuprous iodide was added until a small amount of yellow precipitate was clearly visible, thus ensuring that no excess methyllithium was present. To the resulting lithium dimethylcuprate solution was added a solution of the α,β-unsaturated ketone **10** (35 g, 0.132 mol) in dry ether (1250 ml) over a 20-min period. The reaction was allowed to proceed for an additional 70 min. The cooling bath was removed and a solution of acetyl chloride (187 g, 1.65 mol) in dry ether (1250 ml) was added over a 5-min period. The resulting solution was poured into a rapidly stirred mixture of concentrated ammonium hydroxide and crushed ice, in a ratio of approximately 1:2. The yellow residue which remained in the reaction vessel was destroyed with an additional amount of the ammonium hydroxide–ice mixture, and the resulting solution was added to the preceding mixture. The ether layer was separated and the aqueous solution was extracted once with ether. The combined ether solution was washed with dilute ammonium hydroxide, water, and saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residual material was subjected to column chromatography on 60–100 mesh florisil. The fractions eluted with 1:1 ether–benzene contained 30.6 g (79%) of the enol acetate **11**. The latter fractions were subjected once again to column chromatography and an additional 2.9 g (9%) of compound **11** was obtained. All traces of solvent were removed from the above material under reduced pressure (0.1 mm, 50°) to afford an analytical sample, n^{20}D 1.4987; ir (film) 5.72, 5.93 μ; pmr τ 5.04 (m, 1, vinyl H), 5.37 (m, 1, -OC*H*O-), 7.93 (s, 3, acetate CH_3), 9.05, 9.09 (s, s, 6, tertiary methyls).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.66; H, 9.45.

Preparation of Ketone 12. A solution of 7.46 g (23.2 mmol) of enol acetate **11** and 2.8 g (20.2 mmol) of potassium carbonate in 120 ml of methanol and 20 ml of water was stirred at room temperature for 1 hr. After the solvent had been removed under reduced pressure the remaining residue was diluted with water. The resulting mixture was thoroughly extracted with ether. The combined extracts were washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated. Recrystallization of the residue from hexane afforded 5.1 g (80%) of the ketone **12**: mp 84–86°; ir ($CHCl_3$) 5.88 μ; pmr τ 5.31 (m, 1, -OC*H*O-), 9.02, 9.10 (s, s, 6, tertiary methyls).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 73.00; H, 10.02.

The THP protecting group was removed from the ketone **12** as follows. A solution of 400 mg (1.44 mmol) of compound **12** and 100 mg (1.12 mmol) of oxalic acid in 20 ml of methanol was refluxed for 6 hr. The solvent was removed under reduced pressure,

(32) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

(33) We are very grateful to Professor G. Ourisson for a sample of (−)-seychellene.

and the residue was diluted with water. The resulting mixture was extracted three times with ether. The combined extracts were washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated. Crystallization of the residue from hexane–ether afforded 210 mg (75%) of the corresponding keto alcohol: mp 179–182°; ir ($CHCl_3$) 2.80, 2.95, 5.89 μ; pmr τ 5.85 ("t," 1, -C*H*OH), 9.04 (s, 3, tertiary CH_3 vicinal to OH), 9.08 (d, 3, J = 0.8 Hz, tertiary CH_3 β to carbonyl).[34]

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.59; H, 10.41.

Expoxidation of Enol Acetate 11. A solution of the enol acetate **11** (30.7 g, 0.095 mol) and 68 g (0.356 mol) of 85% *m*-chloroperbenzoic acid in 1500 ml of dry benzene was stirred in the dark for 48 hr. The precipitate was removed by filtration and washed with benzene. The combined filtrate and washings were washed with three portions of 10% aqueous sodium hydroxide. The combined aqueous washings were extracted with ether. The combined benzene solution and ether extracts were washed with water and saturated brine, then dried over anhydrous magnesium sulfate and concentrated under reduced pressure, yielding 30.6 g (95%) of the epoxy acetate **13**. This material could not be purified further since it was heat labile, and unstable to column chromatography. The crude product exhibited the following spectral data: ir (film) 5.74 μ; pmr τ 5.31 (m, 1, -OC*H*O-), 7.05 (s, 1, proton on oxirane ring), 7.95 (s, 3, acetate CH_3), 9.10, 9.18, (s, s, 6, tertiary methyls).

Preparation of Keto Acetate 14. The epoxy acetate **13** (30.6 g) was heated at 160° for 30 min under a nitrogen atmosphere. The resulting material was crystallized from hexane–ether to afford 22.6 g (73%) of the keto acetate **14**: mp 120–123°; ir ($CHCl_3$) 5.80 μ; pmr τ 4.77 (s, 1, -C*H*OAc), 5.34 (m, 1, -OC*H*O-), 7.84 (s, 3, acetate CH_3), 8.53, 8.73 (s, s, 6, tertiary methyls).

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 67.27; H, 8.89.

Removal of the THP Protecting Group from 14. A solution of 400 mg (1.18 mmol) of the keto acetate **14** and a catalytic amount of *p*-toluenesulfonic acid in 25 ml of methanol was heated on a steam bath for approximately 30 min until 10 ml of solvent remained. The remaining solvent was removed under reduced pressure and the residue was diluted with ether. The solution was washed with saturated sodium bicarbonate solution, water, and saturated brine, and then dried over anhydrous magnesium sulfate and concentrated. Crystallization of the residue from ether afforded 240 mg (80%) of the alcohol **15**: mp 195.0–195.5°; ir ($CHCl_3$) 2.78, 2.88, 5.80 μ; pmr τ 4.80 (s, 1, -C*H*OAc), 6.44 (m, 1, -C*H*OH), 7.85 (s, 3, acetate CH_3), 8.59, 8.70 (s, s, 6, tertiary methyls).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72 Found: C, 66.26; H, 8.80.

Preparation of Olefin 16. A stirred suspension of sodium hydride (3.1 g, 0.129 mol) in dry dimethyl sulfoxide (260 ml) was slowly heated, under an atmosphere of nitrogen, to 75°, and kept at this temperature until frothing had ceased (approximately 45 min). The solution was cooled to room temperature and a solution of methyltriphenylphosphonium bromide (53.5 g, 0.15 mol) in dry dimethyl sulfoxide (220 ml) was added. After stirring the reaction mixture for 10 min, a solution of keto acetate **14** (14.5 g, 0.043 mol) in dry dimethyl sulfoxide (340 ml) was added. The reaction mixture was heated at 50° for 2.5 hr, cooled, and diluted with 500 ml of water. The resulting mixture was extracted three times with pentane. The combined extracts were washed twice with water, dried over anhydrous magnesium sulfate, and concentrated. The crude oil was subjected to column chromatography on 60–100 mesh florisil. The fraction eluted with 3:1 benzene-ether contained 10.6 g (73%) of the desired hlefin **16**: n^{20}D 1.4971; ir (film) 3.30, 5.78, 6.08, 11.22 μ; pmr τ 4.63 (m, 1, -C*H*OAc), 5.16, 5.37 (multiplets, 3, =CH_2 and -OC*H*O- overlapping), 7.81 (s, 3, acetate CH_3), 8.73, 8.85 (s, s, 6, tertiary methyls).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.69.

Hydrogenation of Olefin 16. A solution of olefin **16** (6.3 g, 18.8 mmol) and tris(triphenylphosphine)chlororhodium (1.2 g) in benzene (250 ml) was subjected to hydrogenation at room temperature and atmospheric pressure. Hydrogen uptake ceased after approximately 18 hr. The solvent was removed under reduced pressure and 1:1 hexane–ether was added. The precipitate that formed was removed by filtration and the filtrate was chromatographed on a short column of activity II Shawinigan alumina. The desired acetate was eluted with 1:1 hexane–ether. After removal of the solvent under reduced pressure a clear colorless oil remained, which crystallized on standing. Recrystallization from hexane gave 5.7 g (90%) of the desired material **17**: mp 83–86°; ir ($CHCl_3$) 5.77 μ; pmr τ 5.10 (m, 1, -C*H*OAc), 5.30 (m, 1, -OC*H*O-), 7.89, 7.91 (singlets, 3, acetate methyls from two different isomers[19]), 9.03, 9.08 (s, s, 6, tertiary methyls), 9.22 (d, 3, secondary CH_3).

Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 70.68; H, 9.97.

Removal of the THP Protecting Group from 17. The procedure employed for the removal of the THP protecting group was identical with that used for the preparation of compound **15** (*vide supra*). From 388 mg of compound **17** there was obtained, after crystallization from ethyl acetate, 230 mg (89%) of the alcohol **18**: mp 94.5–95°; ir ($CHCl_3$) 2.80, 2.95, 5.81 μ; pmr τ 5.08 (d, 1, J = 2.5 Hz, -C*H*OAc), 5.70 (m, 1, $W_{1/2}$ = 19 Hz, -C*H*OH), 7.91 (s, 3, acetate CH_3), 9.03, 9.14, (s, s, 6, tertiary methyls), 9.23 (d, 3, J = 6 Hz, secondary CH_3).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.55; H, 10.27.

Hydrolysis of the Acetate 17. A solution of the acetate **17** (6.0 g) and potassium hydroxide (24 g) in ethanol (210 ml) and water (24 ml) was refluxed for 4.5 hr. The solvent was removed under reduced pressure and the residue was diluted with water. The resulting mixture was thoroughly extracted with ether. The combined extracts were washed with water and saturated brine, and then dried over anhydrous magnesium sulfate and concentrated. Recrystallization of the residue from hexane yielded 4.42 g (84%) of the alcohol **20**: mp 115–117°; ir ($CHCl_3$) 2.80, 2.95 μ; pmr τ 5.30 (m, 1, -OC*H*O-), 9.11 (d, 3, J = 7 Hz, secondary CH_3), 9.13, 9.17 (s, s, 6, tertiary methyls)

Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.78; H, 10.77.

Removal of the THP Protecting Group from 20. The procedure employed for the removal of the THP protecting group was identical with that used for the preparation of compound **15** (*vide supra*). From 337 mg of alcohol **20** there was obtained, after crystallization from ethyl acetate, 217 mg (90%) of the diol **21**: mp 139.0–139.5°; ir ($CHCl_3$) 2.80, 2.95 μ; pmr τ 5.63 (q, 1, X portion of ABX, J_{AX} = 11 Hz, J_{BX} = 5 Hz, -C*H*(OH)CH_2-), 6.68 (d, 1, J = 3 Hz, -C*H*(OH)CHCH_3), 9.10 (d, 3, J = 7 Hz, secondary CH_3), 9.17 (s, 6, overlapping tertiary methyls).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.66; H, 11.38.

Preparation of Ketone 22. To 100 ml of dry pyridine stirred at 0° was added 4.0 g (40 mmol) of chromium trioxide. To the resulting solution was added 2.96 g (10 mmol) of the crystalline alcohol **20** dissolved in 50 ml of dry pyridine. After the reaction mixture had been allowed to stir at room temperature for 18 hr, water was added and the mixture was extracted three times with ether. The ether solution was concentrated and the residue was diluted with benzene. The benzene solution was washed three times with water and once with saturated brine, and was then dried over anhydrous magnesium sulfate and concentrated. There was obtained a quantitative yield of crude product, which upon crystallization from hexane afforded 1.39 g (47%) of ketone **22**: mp 96–98°; ir ($CHCl_3$) 5.91 μ; pmr τ 5.40 (m, 1, -OC*H*O-), 8.92, 9.01 (s, s, 6, tertiary methyls), 9.03 (d, 3, J = 6.5 Hz, secondary CH_3).

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.55; H, 10.47.

The material obtained from the mother liquors of the above crystallization was subjected to column chromatography on 60-100 mesh florisil. The fractions eluted with benzene contained an additional 0.89 g (30%) of ketone **22**. Although the ir spectrum of this material was virtually identical with the spectrum of crystalline ketone, the oil could not be crystallized. A mixture of the crystalline material and the oil was used for subsequent reactions involving ketone **22**.

Lithium Aluminum Hydride Reduction of Ketone 22. To a stirred solution of 76 mg (2.06 mmol) of lithium aluminum hydride in 10 ml of dry ether was added a solution of 400 mg (1.36 mmol) of ketone **22** in 10 ml of dry ether. The reaction mixture was stirred at room temperature for 3 hr. The excess lithium aluminum hydride was destroyed by careful addition of water, and the resulting mixture was filtered through a sintered glass funnel. The filtrate was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated. In order to remove the THP protecting group, the crude residual material was treated with *p*-toluenesulfonic acid in methanol, as described previously. Re-

(34) *Cf.* K. L. Williamson, T. Howell, and T. A. Spencer, *J. Amer. Chem. Soc.*, **88**, 325 (1966).

crystallization of the product from ethyl acetate afforded 270 mg (92%) of crystalline material which was shown to be identical (melting point, mixture melting point, ir spectrum) with diol **21**, prepared as described above.

Preparation of Tertiary Alcohol 24. To a solution of 3.5 g (13 mmol) of ketone **22** in 25 ml of dry ether was added 11.1 ml of 2.35 *M* methyllithium. The reaction mixture was stirred at room temperature overnight. After careful quenching of the reaction mixture with water, the mixture was thoroughly extracted with ether. The combined extracts were washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated. Since the infrared spectrum of the crude product still showed a weak carbonyl absorption the crude product was once again subjected to reaction with methyllithium as described above, followed by the same work-up procedure. The resulting crude product was subjected to column chromatography on 60–100 mesh florisil. The fractions eluted with 1:1 benzene-ether yielded an oil from which was obtained, by crystallization from hexane, 2.4 g (65%) of the tertiary alcohol **24**, mp 93–95°. The latter fractions from the chromatography still contained some of the starting ketone **22**. This material was therefore again subjected to the original reaction conditions, work-up, and purification to afford an additional 200 mg (5%) of alcohol **24**: ir ($CHCl_3$) 2.80, 2.95 μ; pmr τ 8.23 (s, 3, $-C(OH)CH_3$), 8.65, 8.67 (s, s, 3, tertiary methyls of two epimers[19]), 8.80 (d, 3, J = 6.0 Hz, secondary CH_3), 8.90, 8.92 (s, s, 3, tertiary methyls of two epimers[19]).

Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.30; H, 10.88.

Preparation of Olefin 25. To a stirred solution of alcohol **24** (1.0 g, 3.33 mmol) in dry benzene (15 ml) and dry pyridine (10 ml) at 0° was added, dropwise, a solution of thionyl chloride (322 μl, 4.04 mmol) in benzene (10 ml). The reaction was allowed to proceed for 35 min at 0°. The reaction mixture was poured into rapidly stirred ice water, and extracted three times with benzene. The organic solution was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated to afford a quantitative yield of the olefin **25**. An analytical sample was obtained from column chromatography of the crude product on 60–100 mesh florisil (eluent 4:1 benzene–ether) and exhibited $n^{20}D$ 1.5118; ir (film) 6.15, 11.13 μ. The pmr spectrum was too complex for analysis, probably due to the presence of the THP group, giving rise to an epimeric mixture [19]

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.10; H, 11.03.

Removal of THP Protecting Group from 25. Removal of the tetrahydropyranyl protecting group from compound **25** under the conditions employed previously resulted in partial isomerization of the carbon–carbon double bond. It was found that the protecting group could also be removed by glc; however, this also resulted in partial isomerization of the double bond. Glc analysis of compound **25** employing column A (210°, 100) yielded olefins **27** and **26** in a ratio of approximately 2:3, and when column B (230°, 100) was employed the ratio was reversed to 3:2.

An analytical sample of olefin **26**, collected by glc (column A, 210°, 100) and crystallized from hexane, exhibited mp 69–70°: ir ($CHCl_3$) 2.77, 2.90, 6.13, 11.10 μ; pmr τ 5.14 (m, 2, $=CH_2$), 6.20 (broad m, 1, $-CHOH$), 8.90 (d, 3, J = 6.0 Hz, secondary CH_3), 8.91, 9.05 (s, s, 6, tertiary methyls).

Anal. Calcd for $C_{14}H_{22}O$: C, 80.71; H, 11.61. Found: C, 80.61; H, 11.70

An analytical sample of olefin **27**, collected by glc (column A, 210°, 100) and crystallized from hexane, exhibited mp 104–105°; ir ($CHCl_3$) 2.76, 2.90, 6.12 μ; pmr τ 6.20 (broad m, 1, $-CHOH$), 8.28 (broad s, 6, vinyl methyls), 9.00, 9.03 (s, s, 6, tertiary methyls).

Anal. Calcd for $C_{14}H_{20}O$: C, 80.71; H, 11.61. Found: C, 80.91; H, 11.57.

Preparation of Tosylate 29. To a solution of the crude alkene **25** (1.06 g, 3.66 mmol) in 25 ml of dry tetrahydrofuran under a nitrogen atmosphere was added 7.32 ml of 1 *M* borane in tetrahydrofuran. After the reaction had been allowed to proceed for 2 hr, water was added carefully to destroy the excess borane. To this mixture was added 6 ml of 10% sodium hydroxide solution and 6 ml of 30% hydrogen peroxide solution. The resulting mixture was stirred for 1 hr, diluted with water, and extracted with three portions of methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure, to afford a near quantitative yield of the crude alcohol **28**.

The crude product from the preceding hydroboration was dissolved in 8 ml of dry pyridine and 880 mg (4.63 mmol) of *p*-toluenesulfonyl chloride was added. The reaction mixture was stirred at room temperature for 1.5 hr, cold water was added, and the resulting mixture was thoroughly extracted with ether. The combined organic layer was washed with saturated sodium bicarbonate, water, and saturated brine, dried over anhydrous magnesium sulfate, and concentrated. Crystallization of the crude product from hexane afforded 704 mg of the tosylate **29**. The material obtained from the mother liquors of this crystallization showed an absorption due to the hydroxyl group in the infrared spectrum, and was therefore again subjected to reaction with *p*-toluenesulfonyl chloride as described above. After work-up and crystallization an additional 523 mg of compound **29** was obtained. The overall yield of tosylate **29** from the alkene **25** was 73%. An analytical sample of **29**, obtained by recrystallization of the crude material from ether, exhibited mp 117–117.5°; ir ($CHCl_3$) 6.28, 7.42, 8.54, 10.54 μ; pmr τ 2.15, 2.63 (d, d, 4, J = 8.0 Hz, aromatic protons), 5.37 (m, 1, $-OCHO-$), 7.53 (s, 3, aromatic CH_3), 8.90, 8.94 (s, s, 6, tertiary methyls), 9.12 (d, 3, J = 6.5 Hz, secondary CH_3).

Anal. Calcd for $C_{26}H_{40}O_5S$: C, 67.21; H, 8.68; S, 6.91. Found: C, 67.12; H, 8.55; S, 7.01.

Removal of the THP Protecting Group from 29. The procedure employed for the removal of the tetrahydropyranyl protecting group was identical with that used for the preparation of compound **15** (*vide supra*). From 704 mg of crystalline tosylate **29** there was obtained after crystallization of the crude product from hexane–ether, 310 mg (77%) of the alcohol **30**: mp 117–118°; ir ($CHCl_3$) 3.17, 6.25, 8.51 μ; pmr τ 2.15, 2.62 (d, d, 4, J = 8.0 Hz, aromatic protons), 5.84 (m, 2, $-CH_2OTs$), 6.60 (m, 1, $-CHOH$), 7.53 (s, 3, aromatic CH_3), 8.87, 9.00 (s, s, 6, tertiary methyls), 9.12 (d, 3, J = 6.5 Hz, secondary CH_3).

Anal. Calcd for $C_{21}H_{32}O_4S$: C, 66.28; H, 8.48; S, 8.41. Found: C, 66.11, H, 8.38; S, 8.65.

Preparation of Keto Tosylate 6. To a solution of 400 mg (4.0 mmol) of chromium trioxide in dry pyridine was added a solution of 400 mg (1.1 mmol) of the crystalline alcohol **30** in 2 ml of dry pyridine. After being stirred overnight at room temperature, the reaction mixture was diluted with water and thoroughly extracted with ether. The ether solution was concentrated under reduced pressure and the residue was diluted with benzene. The benzene solution was washed with three portions of water and with one portion of saturated brine, dried over anhydrous magnesium sulfate, and concentrated. Crystallization of the residual material from 100% ethanol afforded 375 mg (94%) of the keto tosylate **6**: mp 108–108.5°; ir ($CHCl_3$) 5.91, 6.28, 8.53 μ; pmr τ 2.14, 2.60 (d, d, 4, J = 8.0 Hz, aromatic protons), 5.84 (m, 2, $-CH_2OTs$), 7.53 (s, 3, aromatic CH_3), 8.97, 9.20 (s, s, 6, tertiary methyls), 9.03 (d, 3, J = 7.0 Hz, secondary CH_3).

Anal. Calcd for $C_{21}H_{30}O_4S$: C, 66.64; H, 7.99; S, 8.45. Found: C, 66.66; H, 7.92; S, 8.65.

Preparation of (±)-Norseychellanone (4). A suspension of sodium hydride (33.6 mg, 1.4 mmol) in 1 ml of dry dimethyl sulfoxide was heated to 75° under a nitrogen atmosphere, and kept at that temperature until frothing had ceased (approximately 45 min). To the resultant solution of methylsulfinyl carbanion was added 267 mg (0.70 mmol) of the keto tosylate **6** in 2 ml of dry dimethyl sulfoxide. The reaction mixture was stirred at 75° for 2 hr, cooled, and diluted with water. The mixture was thoroughly extracted with hexane. The combined extracts were washed twice with water, dried over anhydrous magnesium sulfate, and concentrated. Distillation of the residual oil at reduced pressure gave 131 mg (90%) of (±)-norseychellanone (**4**), bp 120° (bath temperature) (0.2 mm). This material was shown to be one component by glc (column C, 180°, 100, and column A, 200°, 100): ir (film) 5.85 μ; pmr τ 9.03, 9.06 (s, s, 6, tertiary methyls), 9.20 (d, 3, J = 6.5 Hz, secondary CH_3).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.39; H, 10.55.

Preparation of (±)-Seychellene (1). To a solution of 110 mg (0.50 mmol) of (±)-norseychellanone (**4**) in 3 ml of dry ether was added 2.1 ml of 2.35 *M* methyllithium. The resulting solution was refluxed for 2 days. The excess methyllithium was destroyed by careful addition of water, and the aqueous layer was thoroughly extracted with ether. The combined ether extracts were washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The tertiary alcohol **31** thus obtained was dehydrated without further purification.

To a stirred solution of this crude tertiary alcohol **31** in 2.5 ml of benzene and 1.6 ml of dry pyridine at 0° was added 52 μl (0.55 mmol) of thionyl chloride in 1.5 ml of dry benzene. The resulting solution was stirred for 35 min at 0°. The reaction mixture was poured into rapidly stirred ice water and the aqueous layer was

thoroughly extracted with benzene. The combined extracts were washed twice with water and once with saturated brine, and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded a quantitative yield of (±)-seychellene (1). An analytical sample was obtained by preparative glc (column D, 225°, 200), and exhibited spectral data (ir, pmr) and glc retention time (column E, 180°, 90) identical with those of authentic (−)-seychellene: ir (film) 3.26, 6.11, 11.42 μ; pmr τ 5.23, 5.41 (d, d, 2, J = 1.5 Hz, $=CH_2$), 7.78 (m, 1, $-CHC=CH_2$), 9.06, 9.19 (s, s, 6, tertiary methyls), 9.27 (d, 3, J = 6.5 Hz, secondary CH_3).

Mol Wt: Calcd for $C_{15}H_{24}$: 204.188. Found (high-resolution mass spectrometry): 204.188.

Acknowledgments. Financial support from the National Research Council of Canada and the University of British Columbia Committee on Research is gratefully acknowledged. W. de W. is indebted to the National Research Council of Canada for a studentship.

Organometallic Reaction Mechanisms. V. The Mechanism of Dialkylmagnesium Addition to Ketones[1]

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Abstract: The kinetics of the reaction of $(CH_3)_2Mg$ with excess 2-methylbenzophenone was followed spectroscopically by observing the disappearance of absorption bands attributed to complexes of organomagnesium compounds with the ketone and by directly observing the appearance of the product. By using a large excess of ketone, the kinetic order of the organomagnesium species was determined unambiguously to be first order. The reaction of $(CH_3)_2Mg$ with excess ketone was found to consist of a series of pseudo-first-order reactions involving the formation of two intermediate products prior to the formation of the final product

$$\text{reactants} \longrightarrow P_1 \xrightarrow{\text{ketone}} P_2 \xrightarrow{\text{ketone}} P_3 \text{ (final product)}$$

Quenching studies at definite intervals during the reaction have established the formulas of P_1, P_2, and P_3 to be $[CH_3MgOR]_2$, $[CH_3MgOR \cdot Mg(OR)_2]$, and $[Mg(OR)_2]$, respectively (where R = $C(C_7H_7)(C_6H_5)CH_3$). Complexes between the ketone and P_1 and P_2 were observed spectroscopically. The kinetic data can be interpreted in terms of the reaction proceeding through complex formation between the ketone and the organomagnesium species, or in terms of a bimolecular collision not involving the complex. An abbreviated description of the proposed mechanism proceeding through complex can be found below and a more detailed description can be found in the main body of this paper (eq 22–28). The mechanism is as follows: (1) $(CH_3)_2Mg + K \rightleftarrows C \rightarrow P_1$, (2) $P_1 + K \rightleftarrows C_1 \rightarrow P_2$, (3) $P_2 + K \rightleftarrows C_2 \rightarrow P_3$, where K = ketone (2-methylbenzophenone), C = complex between $(CH_3)_2Mg$ and K, $P_1 = (CH_3MgOR)_2$, C_1 = complex between P_1 and K, $P_2 = CH_3MgOR \cdot Mg(OR)_2$, C_2 = complex between P_2 and K, and $P_3 = [Mg(OR)_2]_2$.

The mechanisms of organomagnesium alkylation reactions have been the subject of intensive study for the past decade. In spite of considerable efforts on the part of several groups, there is still no general agreement concerning the manner in which these reactions occur. The principle areas of dispute basically involve the kinetic order of these reactions in organomagnesium reagent, the nature of the reactive species in those cases where several species exist in equilibrium, the exact nature of the alkyl transfer steps, whether they take place by complex formation or by direct bimolecular collision, and finally it is not clear at this time whether the reaction proceeds by a single electron transfer or polar mechanism.

The mechanism receiving the most attention in recent years has been the alkylation of ketones by Grignard reagents. Several mechanisms have been proposed for this reaction. The mechanism proposed by Swain[3] and others[4–6] envisions the rapid formation of a complex between Grignard reagent and ketone followed by a rate-determining attack of a second molecule of Grignard reagent to form product. The dimer mechanism proposed by Bikales and Becker[7] suggests that ketone is attacked by $R_2Mg \cdot MgX_2$ in a bimolecular reaction. This mechanism was supported by the finding that the reaction was initially second order, although rate constants were consistent within each run for only 30% reaction of one alkyl group. Smith and coworkers[8] have offered evidence that Grignard reagents and ketones react immediately to form a complex which then rearranges intramolecularly to give product. The position of Smith and coworkers is supported by a plot of the pseudo-first-order rate constants *vs.* Grignard concentration which is linear for low complex concentrations and extrapolates through the origin. The fact that pseudo-first-order rate constants increase with Grignard concentration is not consistent with the proposed mechanism; however, this observation in regions where all ketone is complexed is justified by Smith by invoking a linear medium effect in order to obtain an empirical fit to the data. It was also not possible for Smith and

(1) We are indebted to the National Science Foundation (Grant No. SP-14795) for partial support of this work.

(2) To whom all inquiries should be sent.

(3) C. G. Swain and H. B. Boyles, *J. Amer. Chem. Soc.*, 73, 870 (1951).

(4) M. Anteunis, *J. Org. Chem.*, 26, 4214 (1961).

(5) E. C. Ashby, R. B. Duke, and H. M. Neumann, *J. Amer. Chem. Soc.*, 89, 1964 (1967).

(6) (a) I. Koppel, L. Margua, and A. Tuulmets, *Reakts. Sposobnost. Org. Soedin.*, 5, 1041 (1968); (b) A. Tuulmets, *ibid.*, 6, 854 (1969).

(7) N. M. Bikales and E. J. Becker, *Can. J. Chem.*, 41, 1329 (1963).

(8) (a) S. C. Smith and G. Su, *J. Amer. Chem. Soc.*, 88, 3995 (1966); (b) J. Billet and S. C. Smith, *ibid.*, 90, 4108 (1968).