

TOTAL SYNTHESSES OF (\pm)-CYCLOSEYCHELLENE AND (\pm)-SEYCHELLENE

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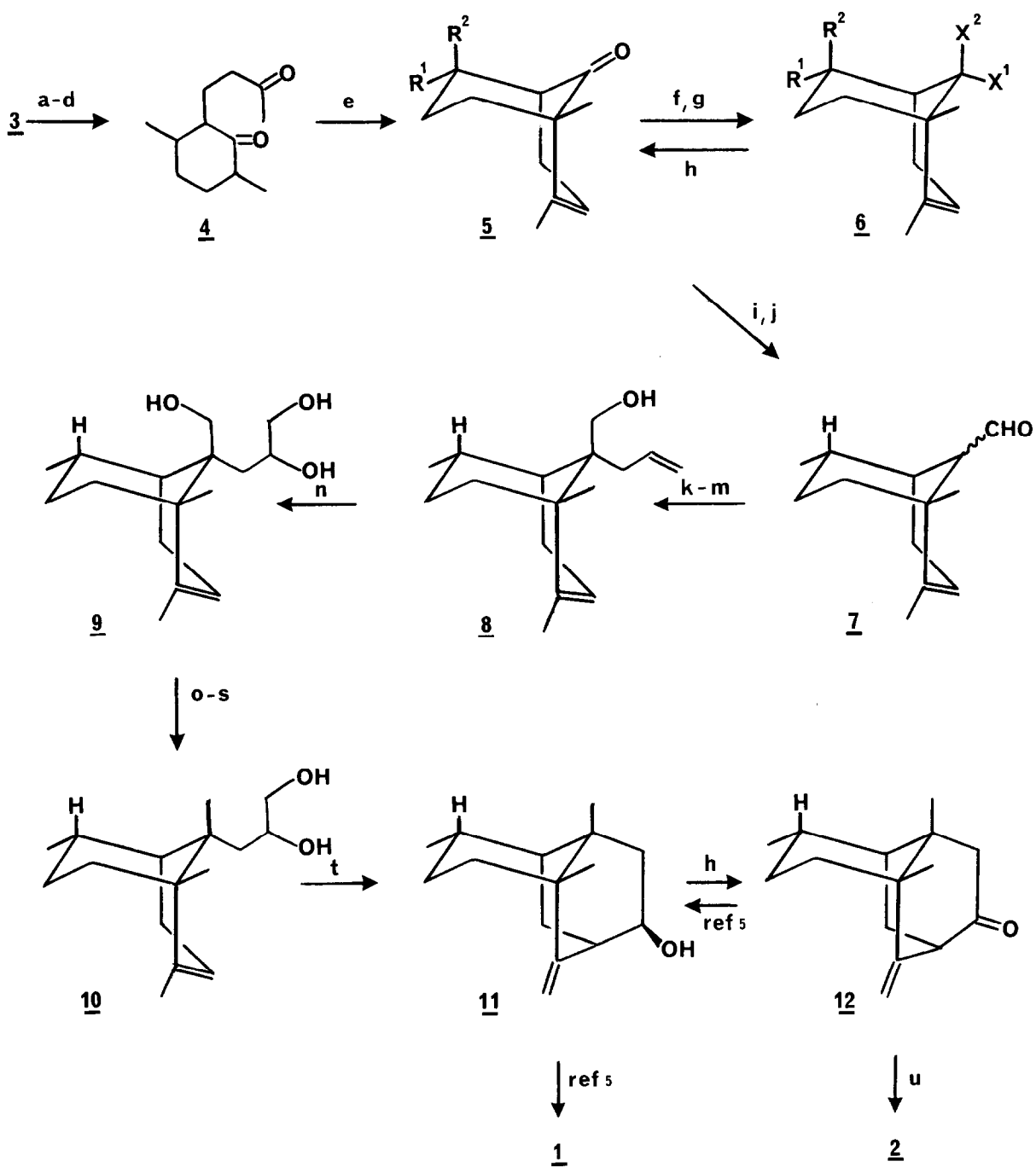
Abstract. Total syntheses of (\pm)-cycloseychellene (1) and (\pm)-seychellene (2) from 2,5-dimethylcyclohexanone (3) are described.

Both the tetracyclic sesquiterpene cycloseychellene (1) and the tricyclic hydrocarbon seychellene (2) were isolated from Patchouli oil (*Pogostemon cablin* Benth.).^{1,2} Recently the structure of cycloseychellene (1)^{3,4} was revised and Yamada and coworkers reported a synthesis of (\pm)-cycloseychellene which confirmed structure 1 for this natural product.⁵

Several successful total syntheses of seychellene (2) have been published.⁶ The purpose of this letter is to present successful total syntheses of (\pm)-cycloseychellene (1) and (\pm)-seychellene (2) via a common intermediate alcohol 11.



Construction of the basic bicyclo[3.3.1]nonane ring skeleton contained within sesquiterpenes 1 and 2 was accomplished by an analogous scheme to that used by Corey and Nozoe in their synthesis of (\pm)-helminthosporal.⁷ Our syntheses commence with the conversion of 2,5-dimethylcyclohexanone (3) to a hydroxymethylene ketone [a) NaH, HCO₂Et, THF; b) H₃O⁺]. Michael reaction of the latter with methyl vinyl ketone [c) MVK, Et₃N] and subsequent decarbonylation [d) K₂CO₃, EtOH, H₂O] produces diketone 4 in 81% overall



yield. Boron trifluoride initiated intramolecular cyclization of 4 to bicyclic ketones 5A and 5E [e] BF_3 (5.4 equiv), CH_2Cl_2 , 0°C -2 h, rt-26 h, conc. 1 g of 4/1.5 L CH_2Cl_2] occurs in 83% yield. Ketones 5A and 5E are produced in a 36:64 ratio of axial $-\text{CH}_3$ ($\text{R}^1=\text{H}$, $\text{R}^2=\text{CH}_3$): equatorial $-\text{CH}_3$ ($\text{R}^1=\text{CH}_3$, $\text{R}^2=\text{H}$) isomers, respectively. These conditions represent a dramatic improvement over those for a similar cyclization reported by Corey and Nozoe.⁷ Reduction of ketones 5AE [f] $\text{Li}(\text{s-Bu})_3\text{BH}$; THF; g) H_2O_2 , OH^-] gives three easily separable isomeric alcohols 6AA [$\text{R}^1=\text{H}$, $\text{R}^2=\text{CH}_3$, $\text{X}^1=\text{H}$, $\text{X}^2=\text{OH}$; 31.4%] 6EA [$\text{R}^1=\text{CH}_3$, $\text{R}^2=\text{H}$, $\text{X}^1=\text{H}$, $\text{X}^2=\text{OH}$; 34.9%]; and 6EE [$\text{R}^1=\text{CH}_3$, $\text{R}^2=\text{H}$, $\text{X}^1=\text{OH}$, $\text{X}^2=\text{H}$; 21.6%].⁸ The stereochemistry of each isomer was established by analysis of the europium-induced NMR shifts⁹ for the secondary methyl group in each isomeric alcohol 6AA, 6EA, and 6EE. Jones' oxidation of 6EA and 6EE [h] H_2CrO_4 , acetone] affords ketone 5E [$\text{R}^1=\text{CH}_3$, $\text{R}^2=\text{H}$] in 84% yield.¹⁰ A Wittig reaction [i] $\text{Ph}_3\text{P}=\text{CHOCH}_3$, Me_2SO] on ketone 5E followed by hydrolysis of the resulting vinyl ether [j] 35% HClO_4 , Et_2O] produces aldehydes 7 in 88% overall yield.¹¹ Alkylation of aldehydes 7 [k] Ph_3CK , DME, Me_2SO cat.; 1) $\text{BrCH}_2\text{CH}=\text{CH}_2$, PhCH_3 , reflux] followed by reduction [m] LiAlH_4 , Et_2O] stereoselectively affords alcohol 8 in 61% overall yield.^{12,13} Selective oxidation of alcohol 8 [n] OsO_4 cat., NMMO (1.15 equiv), THF, H_2O , 26 h] gives triol 9 in 65% yield as a mixture of diastereomers.¹⁴ The glycol was protected [o] acetone, MgSO_4 - CaSO_4 , HCl g cat.] and the primary alcohol was deoxygenated according to the procedure of Ireland and coworkers [p] $n\text{-BuLi}$, THF-hexane, TMEDA; q) $\text{ClPO}(\text{NMe}_2)_2$; r) Li , EtNH_2 , Et_2O , $t\text{-BuOH}$] to produce glycol 10 in 58% overall yield after deprotection [s] 10% HCl , MeOH .^{15,16} Oxidative cleavage of glycol 10 [t] NaIO_4 , THF, H_2O , 20 h] then serendipitously afforded tricyclic alcohol 11 in 77% yield.¹⁷ Apparently the intermediate aldehyde undergoes a facile intramolecular Prins (ene) reaction spontaneously under the conditions of the oxidative cleavage. Yamada and coworkers have already converted alcohol 11 to (\pm)-cycloseychellene (1).⁵ Oxidation of alcohol 11 with Jones' reagent [h] H_2CrO_4 , acetone] gives ketone 12 in quantitative yield.^{5,10} Finally, Wolff-Kishner reduction [u] $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{SO}_4$, KOH , DEG, $23\text{-}200^\circ\text{C}$] of ketone 12 affords (\pm)-seychellene (2) in 73% yield.^{18,19}

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