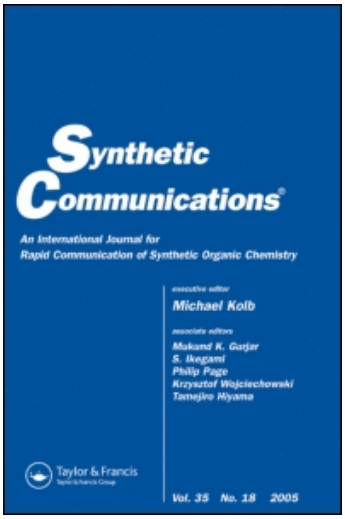

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A SYNTHESIS OF INDAN-BASED PRIMNATRIENE SESQUITERPENE SKELETON

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Abstract A synthesis of densely substituted indane skeleton present in primnatriene sesquiterpenes has been accomplished in a short sequence in which a regioselective Haller-Bauer cleavage of endo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-dione 3 serves as the key step.

In 1988 Cambie et.al., reported from an unnamed soft coral of primnoeides sp., found in the coastal waters of New Zealand, the isolation of five new sesquiterpenoids 1, based on a 2,2,7-trimethyl-4-(1-methylethyl)indane skeleton 2 (Primnatriene).[1] These marine natural products 1 are aromatic analogues of a number of recently isolated bicyclic fungal metabolites[2a] and bear close resemblance to the biologically potent pterosin group of sesquiterpenes.[2b]

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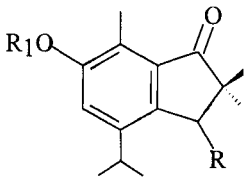
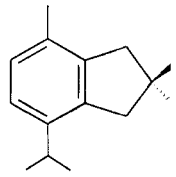
We have recently accomplished the total synthesis of these novel sesuqiterpenes.[3] Concurrently, we have also developed an alternative short, simple route to the indan based primnatriene skeleton 2 present in these sesquiterpenes, through tactical modifications of our earlier approach.[3] These results forms the subject matter of this report.



1

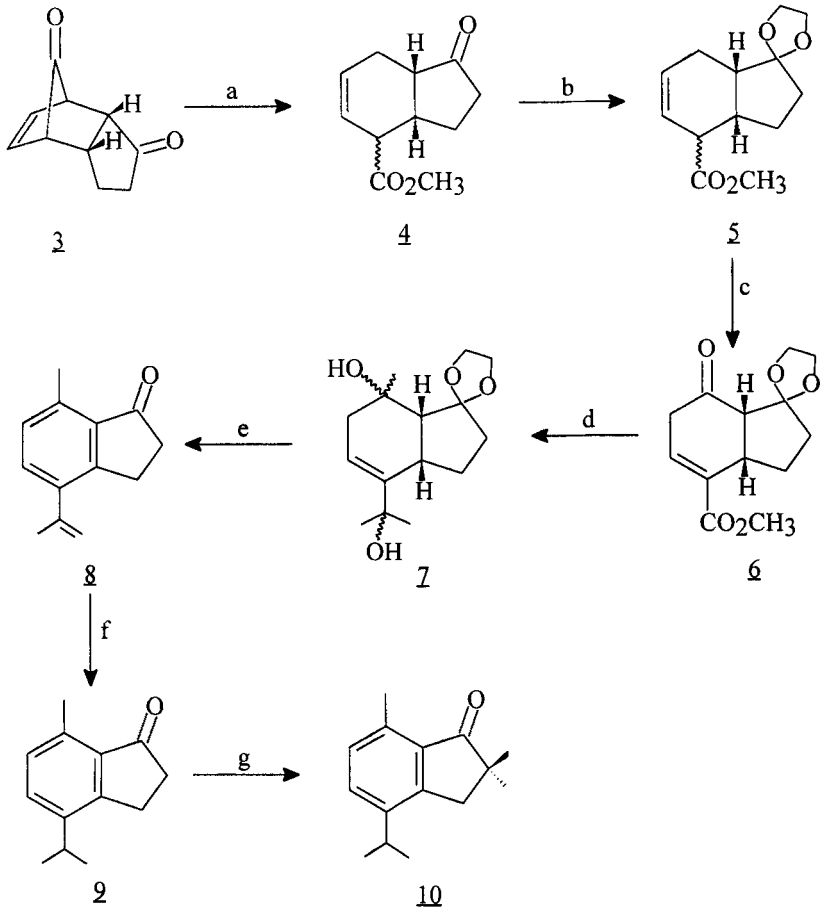
1 a. R=H, R_1=H
b. R=H, R_1=CH_3
c. R=OH, R_1=CH_3
d. R=O, R_1=CH_3
e. R=OAC, R_1=CH_3



2

The cis-fused nonconjugated keto ester 4 was obtained as a diastereomeric mixture through controlled Haller-Bauer cleavage[4] of tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-dione 3 and was considered to be an appropriate precursor for the construction of C_{15} skeleton of primnatriene type sesquiterpenes, *Scheme 1*. Since the stereo centres in 4 were to be eliminated at a later stage we considered it quite appropriate to proceed with the cis-hydrindanone mixture 4 and first converted it to the ketal ester 5. The ketal ester 5, on allylic oxidation with PDC-^{t}BuOOH reagent,[5] quite surprisingly furnished a single conjugated enone 6. Apparently, the β,γ-unsaturated ester is more stable than the corresponding α,β-unsaturated ketone that must be initially formed during the allylic oxidation. When the ester ketone 6 was treated with an excess of methyl lithium, a diol 7 was obtained as a mixture of diastereomers. Thus, three methyl groups were loaded on to the framework of 7 in one step. The tertiary diol 7 was expected to be prone to dehydration and when exposed to PTS-benzene underwent smooth dehydration, oxidative aromatization

Scheme 1



Reagents and Conditions: a) 1% aq. NaOH, benzene, r.t., 24h & CH_2N_2, ether, 30 min, 65-70%; b) $(CH_2OH)_2$, PTS, benzene, reflux, 3 h, 95%; c) PDC, Celite, ^tBuOOH, benzene, r.t., 2h, 60%; d) MeLi, ether, reflux, 2.5h, 60%; e) PTS, benzene, r.t., 6 hr, 30%; f) Pd-C/H_2, ethyl acetate, r.t., 30 min, 90%; g) NaH, MeI, THF, reflux, 3h, 70%.

and ketal deprotection in a one pot reaction to furnish the isopropenylated indanone 8.

The unsaturated indanone 8 on hydrogenation over Pd/C established the isopropyl group in place to yield 9. To complete the acquisition of the C_{15} sesquiterpene skeleton, indanone 9 was subjected to exhaustive methylation to furnish the gem-dimethylated product 10.

In conclusion, we have successfully accomplished a short, convenient synthesis of the primnatriene framework present in a newly discovered family of marine natural products.

EXPERIMENTAL

^1H and ^{13}C samples were made in chloroform-D solvent and were recorded on Bruker AC 200. Chemical shifts are reported in δ scale using tetramethylsilane as the internal standard. Column chromatography was performed using Acme's silica gel (100-200 mesh). All solvent extracts were washed with water, brine, dried over Na_2SO_4 and concentrated at reduced pressure on a Buchi-EL rotary evaporator. Benzene was distilled over sodium and stored over pressed sodium wire. Ethyl acetate was distilled over potassium carbonate. Dry THF was prepared by distillation over sodium-benzophenone ketyl.

exo & endo-Methyl-7-oxocis-bicyclo[4.3.0]non-3-en-2-carboxylate (4): To a solution of 3 (1.25 g, 7.71 mmol) in benzene (50 ml) was added 20 ml of 1% aq.sodium hydroxide and the mixture was stirred at room temperature for 24 h. The benzene layer was separated, the aqueous layer was acidified (pH = 2) and extracted with ethyl acetate (3 x 50 ml). The ethyl acetate extract after washing, drying and removal of the solvent furnished a mixture of acids. To a solution of this mixture of acids in dry ether was added excess of distilled ethereal diazomethane at 0°c till the yellow colour persisted. After 30 min, excess of

diazomethane was destroyed with 2-3 drops of glacial acetic acid. The residue obtained after evaporation of the solvent was charged on a silicagel column and eluted with 30% ethyl acetate-hexane to furnish a mixture of exo- and endo-bicyclic esters 4 (980 mg, 65-70%). ^{1}H NMR: δ 5.89-5.70 (m, 2H, olefinic), 5.68-5.54 (m, 2H, olefinic), 3.69 (s, 3H, ester methyl), 3.68 (s, 3H, ester methyl), 3.18-3.05 (m, 1H), 2.78-2.69 (m, 1H), 2.42-1.82 (m, 6H), 1.61-1.42 9m, 1H); ^{13}C NMR: δ 218.0, 217.0, 173.9, 173.4, 128.3, 127.1, 125.1, 123.0, 52.1, 52.0, 50.0, 49.4, 45.8, 42.1, 40.5, 37.0, 35.0, 27.0, 25.6, 24.8, 20.9.

exo- and endo-Methyl-7,7-(ethylenedioxy)cis-bicyclo[4.3.0]non-3-en-2-carboxylate (5): To a solution of ester mixture 4 (950 mg, 4.85 mmol) in benzene (100 ml) was added ethylene glycol (0.2 ml, 3.6 mmol), catalytic amount of p-toluenesulfonic acid (PTS) and the mixture was refluxed using a Dean-Stark water separator for 3 h. The cooled reaction mixture was washed, dried and the solvent was removed to furnish a mixture of ketals 5 in 95% yield. ^{1}H NMR: δ 5.92-5.79 (m, 2H, olefinic), 5.72-5.59 (m, 2H, olefinic), 3.91-3.85 (m, 8H, ketal), 3.69 (s, 3H, ester methyl), 3.68 (s, 3H, ester methyl), 2.98-2.71 (m, 2H), 2.59-2.42 (m, 1H), 2.20-1.35 (m, 15H); ^{13}C NMR: δ 174.8, 174.1, 128.9, 128.3, 124.4, 122.6, 118.8, 116.6, 64.9, 64.8 (2C), 64.0, 51.9, 51.6, 49.8, 47.8, 43.3, 40.4, 40.1, 36.5, 36.0, 33.4, 27.8, 26.4, 24.2, 21.5.

Methyl-5-oxo-7,7-(ethylenedioxy)cis-bicyclo[4.3.0]non-2-en-2-carboxylate (6): To a solution of 5 (570 mg, 2.39 mmol) in dry benzene (10 ml) was added celite (100 mg), PDC (1.8 g, 4.78 mmol) and 80% ^{t}butylhydroperoxide (215 mg, 2.39 mmol) under nitrogen atmosphere at ice temperature. The reaction mixture was stirred at room temperature for 2 h and then filtered through a small celite pad. Residue obtained after removal of the filtrate was passed through a silica gel (10 g) column. Elution with 35% ethyl acetate-hexane furnished the ester ketone 6 (360 mg) in 60% yield. ^{1}H NMR: δ 6.63-6.61 (m, 1H, olefinic), 4.01-3.85 (m, 4H,

ketal), 3.82 (s, 3H, ester methyl), 2.85-1.40 (series of m, 8H); ^{13}C NMR: δ 200.2, 166.6, 150.7, 134.0, 115.2, 65.4, 65.0, 52.4, 50.2, 40.7, 38.1, 36.2, 26.1; Analysis: $C_{13}H_{16}O_5$, Calcd.: C, 61.89; H, 6.39, Found: C, 61.72; H, 6.32.

2-(1-Hydroxy-1-methylethyl)-5-hydroxy-5-methyl-7,7-(ethylenedioxy)cis-bicyclo[4.3.0]non-2-ene (7): To a solution of 6 (360 mg, 1.42 mmol) in dry ether (10 ml) was added methyllithium in ether (66 mg, 3.02 mmol) under nitrogen. The reaction mixture was refluxed for 2.5 h, then quenched with water and extracted with ethyl acetate. The combined extract was washed and dried. The solvent was evaporated and the residue was filtered through a silica gel (6 g) column by eluting with 50% ethyl acetate-hexane to furnish diol 7 (225 mg, 60%) as a mixture of diastereomers. ^1H NMR: δ 5.67-5.58 (m, 1H, olefinic), 4.02-3.83 (m, 4H, ketal), 2.41-1.42 (series of m, 8H), 1.37 (s, 3h, methyl), 1.34 (s, 3H, methyl), 1.33 (s, 3H, methyl); ^{13}C NMR: δ 148.2, 146.1, 128.5, 126.9, 115.5, 72.8, 72.6, 70.2, 65.1, 64.7, 50.5, 48.2, 42.1, 37.6, 37.2, 36.6, 30.8 , 29.7, 29.6, 28.3, 28.0.

2-(1-Methylethenyl)-5-methyl-7-oxobicyclo[4.3.0]nona-1,3,5-triene (8): To a solution of 7 (210 mg, 0.792 mmol) in dry benzene (4 ml) was added PTS (77 mg, 0.396 mmol) and the mixture was stirred under nitrogen at room temperature. After 6 h, the reaction mixture was diluted with benzene (10 ml), washed and dried. The solvent was evaporated and the residue was filtered through a silica gel (2 g) column. Elution with 20% ethyl acetate-hexane furnished the aromatic ketone 8 (45 mg) in 30% yield. ^1H NMR: δ 7.50 (s, 1H, aromatic), 7.33 (s, 1H, aromatic), 5.29 (s, 1H, exocyclic methylene), 5.10 (s, 1H, exocyclic methylene), 3.16-3.10 (m, 2H), 2.72-2.66 (m, 2H), 2.42 (s, 3H, aromatic methyl), 2.15 (s, 3H, methyl); ^{13}C NMR: δ 207.3, 149.4, 142.8, 141.4, 137.7, 137.4, 134.3, 122.5, 115.8, 36.6, 25.5, 23.5, 21.0; Analysis: $C_{13}H_{14}O$, Calcd.: C, 83.83; H, 7.58, Found: C, 83.79; H, 7.50.

2-(1-Methylethyl)-5-methyl-7-oxobicyclo[4.3.0]nona-1,3,5-triene (9): A solution of 8 (25 mg, 0.134 mmol) in dry ethyl acetate (3 ml) was stirred at room temperature under hydrogen atmosphere over 10% Pd/C (3 mg). After 30 min, the catalyst was filtered and the solvent was evaporated to furnish the aromatic ketone 9 (22 mg) in 90% yield. ^{1}H NMR: δ 7.42 (s, 1H, aromatic), 7.32 (s, 1H, aromatic), 3.12-3.03 (m, 3H), 2.72-2.66 (m, 2H), 2.40 (s, 3H, aromatic methyl), 1.23 (d, J=6.8 Hz, 6H, isopropyl methyl); ^{13}C NMR: δ 207.5, 150.1, 146.1, 137.7, 137.2, 132.0, 121.2, 36.4, 29.6, 23.9, 22.9 (2C), 21.2; Analysis: $C_{13}H_{16}O$, Calcd.: C, 82.93; H, 8.57, Found: C, 82.90; H, 8.51.

2-(1-Methylethyl)-5,8,8-trimethyl-7-oxobicyclo[4.3.0]nona-1,3,5-triene (10): To a solution of 9 (20 mg, 0.106 mmol) in dry THF (3 ml) was added NaH (7.6 mg, 0.318 mmol) and excess methyl iodide under nitrogen atmosphere at room temperature. The reaction mixture was refluxed for 3 h, then quenched with water and extracted with ether (3 x 10 ml). The combined extract was washed and dried. The residue obtained after the evaporation of the solvent was filtered through a silica gel (500 mg) column. Elution with 5% ethyl acetate-hexane furnished the bicyclic ketone 10 (10 mg) in 70% yield. ^{1}H NMR: δ 7.44 (s, 1H, aromatic), 7.34 (s, 1H, aromatic), 3.14-3.00 (m, 1H, hydrogen in isopropyl), 2.93 (s, 2H, a to dimethyl), 2.42 (s, 3H, aromatic methyl), 1.27 (d, J=7 Hz, 6H, isopropyl methyls), 1.24 (s, 6H, dimethyl); ^{13}C NMR: δ 211.7, 147.1, 146.0, 137.9, 135.4, 132.2, 121.9, 45.6, 41.2, 29.6, 25.4 (2C), 22.9 (2C), 21.3; Analysis: $C_{15}H_{20}O$, Calcd.: C, 83.28; H, 9.32, Found: C, 83.21; H, 9.22.

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