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THE STRUCTURE, ABSOLUTE CONFIGURATION AND BIOSYNTHESIS OF NORTILIACORININE A†

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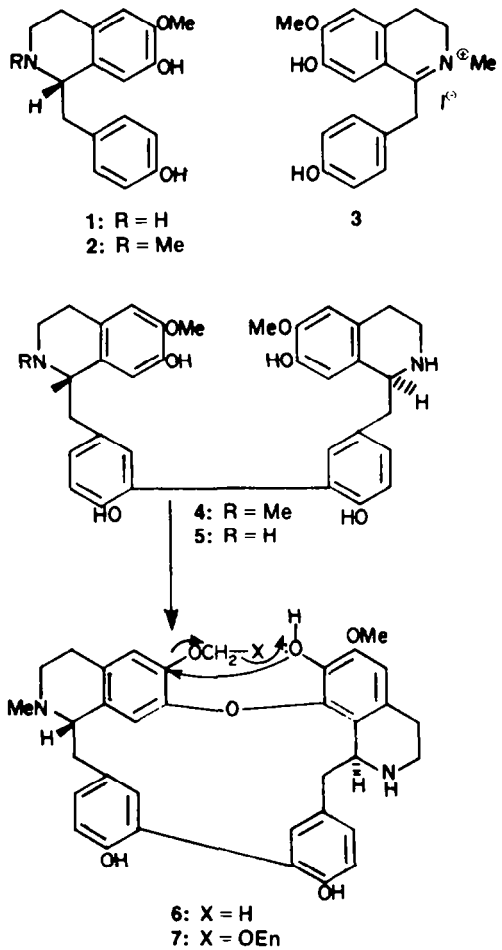
Abstract—The incorporation of (±)-norcoclaurine, (±)-coclaurine, (±)-N-methylcoclaurine and dehydro-N-methylcoclaurine into nortiliacorinine A in *Tiliacora racemosa* colebr has been studied and specific utilisation of the (±)-coclaurine demonstrated. The evidence supports oxidative dimerization of two coclaurine units to give nortiliacorinine A. Experiments with (±)-N-methylcoclaurine and (±)-[1-^{3}H, N-^{14}CH$_3$]N-methylcoclaurine established that only one N-methylcoclaurine unit is specifically utilised to constitute that "half" of the base which had phenolic OH group in the benzylic portion and further demonstrated that the H atom at the asymmetric centre in the 1-benzylisoquinoline precursor is retained in the bioconversion into nortiliacorinine A. Double labelling experiment with (±)-[1-^{3}H, 6,0-^{14}CH$_3$]N-methylcoclaurine showed that O-Me function of the precursor is lost in the bioconversion into nortiliacorinine A. Parallel feedings of (+)-(*S*)- and (−)-(*R*)-N-methyl-coclaurines and (−)-(*S*)-, and (+)-(*R*)-coclaurines revealed that the stereo-specificity is maintained in the biosynthesis of nortiliacorinine A from 1-benzylisoquinoline precursors and established '*S,S*'-configuration at the two asymmetric centres in nortiliacorinine A.

Isomeric bases nortiliacorinine A and nortiliacorinine B isolated from *Tiliacora* species[1-3] were assigned the structure (**9** or **10**, without stereochemistry). The position of N-Me group and stereochemistry at the two asymmetric centres in these bases were not defined. Both the bases, however, when treated separately with formaldehyde–formic acid furnished the same N-Me derivative identical with tiliacorinine.[4] The absolute configuration at the asymmetric centres in nortiliacorinine A type bases can not be determined by the usual sodium/liquid ammonia fission method[5] because the lower rings of these biphenyl bisbenzylisoquinoline alkaloids are linked through a direct C–C bond, rather than through the much common diaryl ether bridge. This unusual structural feature present in these alkaloids precludes facile chemical interrelationship between nortiliacorinine type bases and other bisbenzylisoquinolines of established structure and stereochemistry.[6]

It has been shown by tracer experiments that the bisbenzylisoquinoline alkaloids epistephanine,[7] cocsulin,[8] cocsulinine,[9] tiliacorine,[10] tiliacorinine[10] and tiliageine[11] are formed in nature from coclaurine derivatives. Nortiliacorinine A and nortiliacorinine B can similarly form in nature from coclaurine derivatives. Oxidative dimerization[12] of coclaurine (**1**) can give the dimeric base (**5**). Compound **5** can undergo intramolecular oxidative coupling to give **6**. Elimination of the OMe group from the isoquinoline portion of **6**, probably as formaldehyde or its equivalent, can then generate dibenzo-*p*-dioxin system. Finally selective N-, and O-, methylation can yield nortiliacorinine A and nortiliacorinine B. Alternatively intermolecular oxidative coupling of coclaurine (**1**) and N-methylcoclaurine (**2**) can give the dimeric intermediate (**4**) which can modify as above to form nortiliacorinine A and nortiliacorinine B. In the third possibility N-methylcoclaurine (**2**) can undergo oxidative dimerization to give the dimeric intermediate. Intermolecular oxidative coupling, selective N-demethylation and elimination of OMe group from the isoquinoline portion as above can yield bases of nortiliacorinine A type.



Initially labelled tyrosine was fed to young *Tiliacora racemosa* colebr (menispermaceae) and it was found that

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Table 1. Tracer experiment on *T. racemosa*

Expt.	Precursor Fed	Incorporation % into Nortiliacorinine A
1	(L)-[U-^{14}C] Tyrosine	0.094
2	(±)-[1-^{3}H] Norcoclaurine(13)	0.14
3	(±)-[3',5', 8-$^{3}H_3$] Coclaurine(14)	0.20
4	(±)-[3',5', 8-$^{3}H_3$] N-Methylcoclaurine(15)	0.24
5	(±)-[3',5', 8-$^{3}H_3$] NOO-Trimethylcoclaurine	0.0005
6	Dehydro-[N-methyl-^{14}C] N-methylcoclaurinium iodide(3)	0.15
7	(±)-[1-^{3}H, N-methyl-^{14}C]N-methylcoclaurine(15) ratio(^{14}C:^{3}H, 1:30)	0.26 (^{14}C:^{3}H, 1:28)
8	(±)-[1-^{3}H, 6-methoxy-^{14}C] N-methylcoclaurine(15) ratio(^{14}C:^{3}H, 1:24)	0.24 (^{14}C:^{3}H, 1:44)
9	(-)-(R)-[3',5', 8-$^{3}H_3$] N-Methylcoclaurine	0.0006
10	(+)-(S)-[3',5', 8-$^{3}H_3$] N-Methylcoclaurine(2)	0.30
11	(-)-(S)-[3',5', 8-$^{3}H_3$] Coclaurine(1)	0.36
12	(+)-(R)-[3',5', 8-$^{3}H_3$] Coclaurine	0.0038

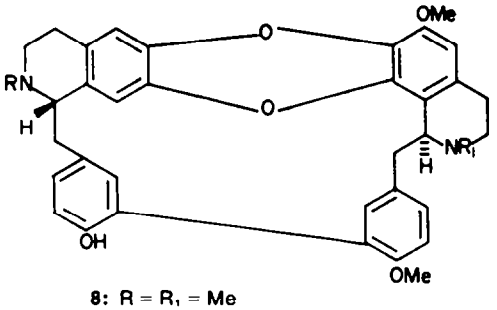
nortiliacorinine A was being actively biosynthesised by the plants. In subsequent experiments labelled hypothetical 1-benzyltetrahydroisoquinoline precursors were fed to young *T. racemosa*. The results of several feedings are recorded in the Table 1. Feeding of (±)-norcoclaurine (**13**, Expt **2**), (±)-coclaurine (**14**, Expt. 3), (±)-N-methylcoclaurine (**15**, Expt. 4) demonstrated that **13**, **14** and **15** were metabolised by the plants to form nortiliacorinine A. The completely methylated 1-benzyltetrahydroisoquinoline, (±)-NOO-tri-methylcoclaurine (Expt. 5), as expected, was not utilized by the plants to form nortiliacorinine A.

Labelled nortiliacorinine A derived from (±)-[3',5',8-$^{3}H_3$] coclaurine (**14**, Expt. 3) was treated with formaldehyde–formic acid to give tiliacorinine (**8**) which had essentially the same radioactivity as the parent base. Treatment of radioactive **8** with MeI in the presence of sodium methoxide furnished O-methyltiliacorinine dimethiodide with essentially no loss of radioactivity. Oxidation of the radioactive dimethiodide with alkaline permanganate followed by methylation of the acids, thus formed, by diazomethane yielded 5,5' - dicarbomethoxy - 2,2' - dimethoxydiphenyl (**11**) and 3,4,7,8 - tetracarbomethoxy - 1 - methoxydibenzo - *p* - dioxin (**12**). The former had essentially 2/3 and the latter 1/3 radioactivities of the parent base. The results, thus, established that both the "halves" of nortiliacorinine A were formed from coclaurine in *T. racemosa* plants.

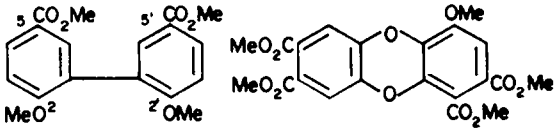
The specific incorporation of N-methylcoclaurine (**15**) into nortiliacorinine A was demonstrated as follows: biosynthetic nortiliacorinine A derived from (±)-[3',5',8-$^{3}H_3$] N-methylcoclaurine (Expt. 4) was treated with formaldehyde–formic acid to give tiliacorinine A (**8**) with essentially no loss of radioactivity. Treatment of radioactive **8** with MeI gave tiliacorinine dimethiodide. Alkaline permanganate oxidation of the radioactive dimethiodide which destroyed the benzene ring containing phenolic OH groups yielded the acids. Methylation of the acids with diazomethane afforded dimethyl 4-methoxyisophthalate (**16**) and **12**. Compound **12** had essentially one half the radioactivity of the parent base whereas **16** was practically radioinactive. The results established that only one N-methylcoclaurine (**15**) unit was specifically utilised by the plants to form nortiliacorinine A. The results further demonstrated that the N-Me and phenolic OH groups were on the same "half" of the molecule. The structure of nortiliacorinine A should, therefore be, **9** (without stereochemistry) and that of nortiliacorinine B as **10** (without stereochemistry). The structure **9** for nortiliacorinine A was further confirmed by experiments with double labelled precursors. Feeding of (±)-[1-^{3}H, N-$^{14}CH_3$] N-methylcoclaurine (**15**, Expt. 7) gave nortiliacorinine A labelled both with ^{14}C and ^{3}H. Moreover, the ^{14}C and ^{3}H ratios in the precursor and biosynthetic base were essentially unchanged. Obviously N-methylcoclaurine (**15**) was not being N-demethylated to give coclaurine (**14**) to construct the other "half" of the molecule.

Nortiliacorinine A had a dibenzo-*p*-dioxin system. According to the biogenetic proposals[6,13] the OMe function from the N-methylcoclaurine (**15**) unit should be eliminated during the biotransformation of the precursor into the product. Feeding of (±)-[1-^{3}H, 6-methoxy-^{14}C] N-methylcoclaurine (Expt. 8) yielded nortiliacorinine A labelled only with tritium. The results were thus in conformity with the biogenetic proposal.

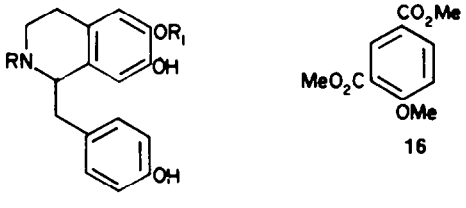
The foregoing experiments established the structure **9** (without stereochemistry) for nortiliacorinine A. Nortiliacorinine A had two asymmetric centres. The configuration at these centres can be either "*R,S*" or "*S,S*" or "*S,R*" or "*R,R*". Tracer experiments with [1-^{3}H, N-$^{14}CH_3$] N-methylcoclaurine (Expt. 8) revealed that the H atom at the asymmetric centre in 1-benzyltetrahydroisoquinoline precursor was not touched in the biotransformation of the precursor into nortiliacorinine A. Parallel feedings with (+)-(*S*)-N-methylcoclaurine (**2**, Expt. 10) and (−)-(*R*)-N-methylcoclaurine (Expt. 9) demonstrated that **2** was exclusively incorporated into nortiliacroinine A. Parallel feedings with (−)-(*S*)-coclaurine (**1**, Expt. 11) and (+)-(*R*)-coclaurine (Expt. 12) confirmed that nortiliacorinine A was stereospecifically biosynthesised from (−)-(*S*)-



8: R = R₁ = Me
9: R = Me; R₁ = H
10: R = H; R₁ = Me



11 12



13: R = R₁ = H
14: R = H; R₁Me
15: R = R₁ = Me

16

coclaurine (1). The results, thus, confirmed "*S,S*"-configuration at the asymmetric centres in nortiliacorinine A.

Coclaurine (1) was stereospecifically incorporated into nortiliacorinine A in *T. racemosa*. The presence of 1 in the plants was established by trapping experiments. Coclaurine (1) was, thus, the true precursor of nortiliacorinine A (9) in *T. racemosa*. The foregoing results strongly supported the following sequence for the biosynthesis of nortiliacorinine A in *T. racemosa*: Tyrosine → norcoclaurine → (*S*)-coclaurine-(dimerization) → nortiliacorinine A.

EXPERIMENTAL

For general directions (spectroscopy details and counting method) see Ref. 9.

Synthesis of precursors. The racemates of norcoclaurine, compounds **14** and **15** were prepared by the known procedures.

Resolution. The salt of (±)-O,O-dibenzylcoclaurine (1.75 g) and (+)-di-*p*-toluoyltartaric acid (1.45 g) was fractionally crystallized from EtOH–Et_2O, EtOH and MeOH to give the salt (1.5 g) m.p. 156–158°; $[\alpha]_D$ 86° (*c*, 1.0). This salt was treated with 4N NaOH and the (+)-O,O-dibenzylcoclaurine, so obtained, was chromatographed over Al_2O_3. The pure product was crystallised from EtOH as plates m.p. 89–89°; $[\alpha]_D$ + 15° (*c*, 0.5 in MeOH) and − 26° (*c*, 0.5 in $CHCl_3$) (lit.[17] 83–89°; $[\alpha]_D$ − 25° in $CHCl_3$).

(−)-(S)-*Coclaurine hydrochloride.* (+)-O,O-Dibenzylcoclaurine was heated with 30% HCl in EtOH at 100° for 1 hr. The resulting (−)-*coclaurine* HCl crystallised from EtOH as needles, m.p. 166–168°. After drying at 100° *in vacuo* had m.p. 262–263°; $[\alpha]_D$ − 15° (*c*, 1.2 MeOH). The free base had m.p. 264–265°; $[\alpha]_D$ − 18° (*c*, 1.0 in MeOH) (lit.[17] 263–264°; $[\alpha]_D$ − 13° in MeOH).

(−)-O,O-*Dibenzylcoclaurine.* O,O-Dibenzylcoclaurine (0.9 g) enriched with the (−)-enantiomer was treated with (−)-di-*p*-toluoyl-*d*-tartaric acid (0.78 mg) to give (−)-O,O-*dibenzylcoclaurine* (325 mg), as plates m.p. 86–87°, $[\alpha]_D$ − 16° (*c*, 0.5 in MeOH); $[\alpha]_D$ + 23° (*c*, 0.6 in $CHCl_3$) (lit.[17] 87–88°, $[\alpha]_D$ − 15° (*c*, 0.5 in MeOH).

(+)-(R)-*Coclaurine hydrochloride.* (−) - O,O - Dibenzylcoclaurine (310 mg) was hydrogenolysed with 30% HCl in the usual way to give (+)-*coclaurine* HCl (135 mg) m.p. 262–264°; $[\alpha]_D$ + 15° (*c*, 1.2 in MeOH) (lit.[17] 261–263°).

Tritiation labelling of precursors. (±)-Coclaurine hydrochloride (130 mg) in tritiated H_2O (0.5 ml, 80 mCi) containing *t*-BuOK (220 mg) was heated under N_2 (sealed tube) for 100 hr at 100° to give (±)-[3′,5′, 8-$^3H_3$] *coclaurine* which was purified as its hydrochloride (90 mg) and crystallized from MeOH to constant activity. The other 1-benzyltetrahydroisoquinoline precursors were tritiated in the similar manner.

(±)-[1-^{3}H] Norcoclaurine and (±)-[1-^{3}H] N-methylcoclaurine were prepared by reduction of the corresponding dihydroisoquinolines with potassium-[^{3}H]-borohydride in dry DMF. (±)-[N-$^{14}CH_3$] N-Methylcoclaurine and dehydro - N - [^{14}C]methyl - coclaurinium salt were prepared by treating the corresponding dihydroisoquinolines *χ* with [^{14}C] MeI and subsequent reduction of the methiodide with $NaBH_4$. (±)-[6-methoxy-^{14}C] coclaurine was prepared by complete synthesis. (±)-[3′, 5′, 8 - $^3H_3$] N-Methylcoclaurine was treated with diazomethane to give (±) - [3′, 5′, 8 - $^3H_3$] NOO-trimethylcoclaurine.

Doubly labelled (±) - [1 - ^{3}H, 6 - methoxy - ^{14}C] N-methylcoclaurine was prepared by mixing (±)-N-Methyl[1-^{3}H] coclaurine and (±)-[6-methoxy - ^{14}C] N-methylcoclaurine. (±) - [N - methyl - ^{14}C] N-methyl[1 - ^{3}H] coclaurine was prepared by mixing (±) - N - methyl[1-^{3}H] coclaurine and (±)-[N-methyl-^{14}C] N-methylcoclaurine.

Feeding experiments. N-Methylcoclaurine and N,O,O-trimethylcoclaurine were dissolved in H_2O (1 ml) containing tartaric acid (10 mg). Coclaurine hydrochloride, dehydro-N-methylcoclaurinium iodide and norcoclaurine hydrochlorides were dissolved in H_2O (1 ml) containing DMSO (0.2 ml). The soln of the precursors was introduced into young *T. racemosa* plants by wick feeding. When uptake was complete the plants were left for 8 to 10 days to metabolise the precursor and then worked up for nortiliacorinine A.

Isolation and purification of nortiliacorinine A. Young plants (typically 120 g wet wt) of *T. racemosa* fed with precursor were macerated in EtOH (300 ml, containing 1% AcOH) with radioinactive nortiliacorinine A (80 mg) and left for 12 hr. The plant material was extracted with EtOH (6 × 200 ml, containing 1% AcOH). The ethanolic extract was concentrated *in vacuo* to afford a greenish viscous mass which was extracted with H_2O (3 × 10 ml). The residual material was further extracted with 2% AcOH (3 × 10 ml). The aqueous acidic extract was defatted with Et_2O (4 × 20 ml), basified with Na_2CO_3 and the liberated bases extracted with $CHCl_3$ (5 × 15 ml). The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4) and the solvent removed. The crude bases (90 mg), so obtained, were chromatographed over neutral Al_2O_3. Elution with C_6H_6–$CHCl_3$ (1:1) gave a product which was subjected to preparative tlc on SiO_2 plates (Solvent: $CHCl_3$–MeOH, 95:5) to give **9** (68 mg) m.p. 252–253° (lit.[3] 252–253°). The base was crystallised from $CHCl_3$-acetone to constant activity.

Degradation of nortiliacorinine A derived from (±)-[3′, 5′, 8 - $^3H_3$] *coclaurine.* Labelled **9** (300 mg; molar activity 6.93×10^{-2} μCi mmol^{-1}) (Expt. 3) was treated with HCO_2H (100%, 5 ml) and HCHO (38%, 3 ml) to give radioactive **8** (258 mg) m.p. 194° (molar activity 6.90×10^{-2} μCi mmol^{-1}), (lit.[1] 195°).

A suspension of the preceding radioactive **8** (250 mg) in MeOH (50 ml) was heated with MeONa and MeI (3 ml) to give radioactive O-*methyltiliacorinine dimethiodide* (300 mg) m.p. 272–275° (lit.[1] 270–275° (molar activity 6.86×10^{-2} μCi mmol^{-1}).

An aqueous soln of $KMnO_4$ (4%, 100 ml) was added dropwise to a stirred soln of the preceding radioactive O-methyltiliacorinine dimethiodide (300 mg) in H_2O at 70–80°. The mixture was kept at 70–80° for 5 hr. The MnO_2 ppt from the resulting mixture was filtered off. The filtrate was concentrated under reduced pressure to 5 ml and acidified with conc HCl. The

Table 2. Radioactivity of the degradation products of the biosynthetic nortiliacorinine A (Expt. 10)

Compound	Molar activity (μCi m mol^{-1})
Nortiliacorinine A (9)	7.72×10^{-2}
Tiliacorinine (8)	7.60×10^{-2}
Tiliacorinine dimethiodide	7.55×10^{-2}
3,4,7,8-Tetracarbomethoxy-1-methoxydibenzo-p-dioxin (12)	3.87×10^{-2}
Dimethyl-4-methoxyisophthalate	inactive

Table 3. Radioactivity of the degradation products of the biosynthetic nortiliacorinine A (Expt. 11)

Compound	Molar activity (μCi m mol^{-1})
Nortiliacorinine A (9)	10.39×10^{-2}
Tiliacorinine A (8)	10.30×10^{-2}
O-Methyltiliacorinine dimethiodide	10.20×10^{-2}
5',5'-Dicarbomethoxy-2,2'-dimethoxydiphenyl (11)	6.82×10^{-2}
3,4,7,8-Tetracarbomethoxy-1-methoxydibenzo-p-dioxin (12)	3.38×10^{-2}

liberated acid A (60 mg) was filtered off. The filtrate was kept for the isolation of the acid B.

The crude radioactive acid A (58 mg) in MeOH (2 ml) was treated with an excess of ethereal CH_2N_2 to give the radioactive *5,5'-dicarbomethoxy-2,2'-dimethoxydiphenyl* **11** (25 mg), m.p. 173–174° (lit.[1] 172–173°) (molar activity 4.58×10^{-2} μCi mmol^{-1}). Water from the filtrate containing the acid B was removed *in vacuo*. The residue, so obtained, was suspended in MeOH (2 ml) and to it was added an excess of ethereal CH_2N_2 to give radioactive 3,4,7,8 - *tetracarbomethoxy* - 1 - *methoxy* - *dibenzo* - p - *dioxin* **12** (10 mg), m.p. 179–180° (lit.[1] 180–181°) (molar activity 2.22×10^{-2} μCi mmol^{-1}).

Degradation of nortiliacorinine A derived from (±)-[3',5',8-$^3H_3$] N-*methylcoclaurine*. Labelled nortiliacorinine A (380 mg) (molar activity 21.60×10^{-2} μCi mmol^{-1}) (Expt. 4) was treated with HCO_2H-HCHO as above to give radioactive **8** (350 mg; molar activity 21.50×10^{-2} μCi mmol^{-1}).

A mixture of the preceding radioactive **8** (350 mg) and MeI (2 ml) in $CHCl_3$ (10 ml) was left at room temp for 30 hr to give radioactive *tiliacorinine dimethiodide* (370 mg) m.p. > 300° (lit.[1] > 300°) (molar activity 21.61×10^{-2} μCi mmol^{-1}).

The preceding radioactive tiliacorinine dimethiodide (360 mg) in H_2O (25 ml) at 75° to 80° was oxidised with 4% $KMnO_4$ aq. (60 ml) as above to give *dimethyl* - 4 - *methoxyisophthalate* (**16**) m.p. 94° (lit.[1] 95°) which was essentially radioinactive and 3,4,7,8 - *tetracarbomethoxy* - 1 - *methoxydibenzo* - p - *dioxin* **12** (10 mg) (molar activity 10.42×10^{-2} μCi mmol^{-1}).

Degradation of nortiliacorinine A derived from (+)-(S)-[3',5',8-$^3H_3$] N-*methylcoclaurine*. Labelled nortiliacorinine A (Expt. 10) was converted into radioactive *tiliacorinine dimethiodide* and then oxidised with $KMnO_4$, as above, to give radioinactive **16** and **12**. The radioactivity of the degradation products is given in the Table 2.

Degradation of nortiliacorinine A derived from (−)-(S)-[3',5',8-$^3H_3$] *coclaurine*. Labelled nortiliacorinine A (360 mg) (Expt. 11) was converted into radioactive O-*methyltiliacorinine dimethiodide* which was oxidised with $KMnO_4$ to give radioactive 3,4,7,8 - *tetracarbomethoxy* - 1 - *methoxy* - *dibenzo* - p - *dioxin* **12** (15 mg) and 5,5' - *dicarbomethoxy* - 2,2' - *dimethoxydiphenyl* **11**. The radioactivity of the degradation products is given in the Table 3.

Trapping experiments. (L)-[U-^{14}C] Tyrosine (activity 0.1 mCi) in H_2O (1 ml) was fed to young *T. racemosa*. The plants were kept alive for 8 days and then harvested. (±)-N-*Methylcoclaurine* **15** (110 mg) was added to the macerated plant material and kept in EtOH containing 1% AcOH (250 ml) for 12 hr. The EtOH was decanted and the plant material was percolated with fresh EtOH containing 2% AcOH (6 × 200 ml). The ethanolic extract was concentrated *in vacuo* to give a greenish viscous mass which was extracted with 3% AcOH (6 × 10 ml). The aqueous acidic extract was defatted with Et_2O and basified with $NaHCO_3$ aq. The liberated bases were extracted with $CHCl_3$ (5 × 15 ml), washed with H_2O and solvent removed. The crude base, so obtained, was subjected to preparative tlc on SiO_2 plates to give (±)-N-*methylcoclaurine* **15** (600 mg) (molar activity 1.01 μCi mmol^{-1}); incorporation 0.43%.

In another experiment, (L)-[U-^{14}C] tyrosine (activity 0.1 mCi) was fed to young *T. racemosa*. After 10 days the plants were killed and harvested. (±) **14** (123 mg) was added and reisolated as above to give radioactive (±)- **14** (72 mg; molar activity 10.27×10^{-2} μCi mmol^{-1}); incorporation 0.32%.

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