Table I. Physical and Spectral Data for Uskudaramine and Derivative

Uskudaramine (1)

UV (MeOH) λ_{max} 209 nm, 221 (sh), 286, 300 (sh), 312 (sh) (log ϵ 4.78, 4.73, 4.35, 4.18, 4.06); UV (MeOH-OH^-) λ_{max} 210 nm, 262 (sh), 303, 321 (sh) (log ϵ 4.90, 4.26, 4.37, 4.20); MS, *m/z* 668 (M^+, 0.1), 667 (0.1), 608 (0.3), 476 (3.3), 461 (1.2), 460 (2.6), 446 (1.8), 416 (0.7), 192 (100), 177 (13); CD (MeOH) $\Delta\epsilon$ (nm) −4.8 (297), −3.9 (280), +48 (244), −32 (212); $[\alpha]^{25}_D$ +84° (*c* 0.15, MeOH)

Triacetyluskudaramine

NMR (200 MHz, FT, $CDCl_3$) δ 1.96, 2.04, 2.26 (3 × 3 H, s, 3 acetyls), 2.46 (6 H, s, 2 NCH_3), 3.79, 3.80, 3.90, 3.91, 3.96 (5 × 3 H, s, 5 OCH_3), 6.40 (1 H, s, H-8′), 6.64 (1 H, s, H-5′), 7.00-7.20 (3 H, m, H-10′, H-13′, H-14′), 8.11 (1 H, s, H-11); MS, *m/z* 794 (M^+, $C_{45}H_{50}O_{11}N_2$, 0.1), 752 (0.2), 709 (0.1), 560 (0.4), 518 (1.4), 477 (2.4), 446 (1.3), 434 (1.4), 234 (100), 192 (81), 177 (5)

In order to provide additional support for the presence of the phenolic function at C-9, we treated the new alkaloid with acetic anhydride in pyridine to yield the corresponding triacetate ester, $C_{45}H_{50}O_{11}N_2$, whose NMR spectrum displays a downfield shift of H-11 from δ 7.99 to 8.11 (Table I). It follows that in species 1 a phenolic group must be present in the same aromatic ring as H-11, more specifically at C-9.

To further ascertain the structure of the new alkaloid, we carried out an NMR NOE study on a deoxygenated deuteriochloroform solution of the alkaloid, the results of which have been summarized in expression **1a**.[5] The relative position of each of the six aromatic protons was determined in relation to each of the methoxyl substituents. Separate irradiations of the aromatic hydrogens substantiated the fact that all of these protons belong to the benzylisoquinoline moiety except for H-11 (δ 7.99) whose irradiation produces a 2% NOE of the C-1 methoxyl (δ 3.73) and a 4% NOE of the C-10 methoxyl (δ 3.97). It should be pointed out as an aside that, in the NMR spectrum of uskudaramine (1), the chemical shift of H-11 at δ 7.99 is in keeping with the presence of a substituent at C-3 of the aporphine, since if C-3 were unsubstituted H-11 would have appeared downfield from δ 8.10.[2]

Other significant NMR NOE findings are that irradiation of H-8′ (δ 6.28) caused a 1% dipole-dipole relaxation enhancement of H-10′ (δ 6.78) and a 2% enhancement of the H-1′ signal (δ 3.67), while irradiation of H-10′ led to a 1% enhancement of H-8′. These NOE results not only confirm the structure of the alkaloid but also lead to some understanding of the conformation of the molecule.

The CD spectrum of (+)-uskudaramine (1), with a Cotton effect maximum at 244 nm and a negative trough at 212 nm (Table I), is very close to that of (+)-istanbulamine (**2**),[2] and generally resembles that of alkaloids belonging to the (+)-thalicarpine (**3**) series. All of these dimers thus possess the identical absolute configuration.[6]

The importance of (+)-uskudaramine (1) resides partly in the fact that it is the first among some 35 aporphine-benzylisoquinoline alkaloids known[6] whose two constituent entities are bonded together directly through carbon to carbon coupling rather than the much more usual oxygen to carbon linkage.

(+)-Uskudaramine (1) and (+)-istanbulamine (**2**) are accompanied in the plant by the (+)-thalicarpine (**3**) analogues (+)-*N*-2′-noradiantifoline, (+)-adiantifoline, and (+)-thaliadanine. All of these bases incorporate a methoxyl group at C-10. They are formed by direct oxidative coupling of a fully evolved 1,2,9,10-tetraoxygenated or 1,2,3,9,10-pentaoxygenated aporphine derived from (+)-reticuline with a tetrahydrobenzylisoquinoline.[2] In the case of (+)-uskudaramine and (+)-istanbulamine, this tetrahydrobenzylisoquinoline is (+)-*N*-methylcoclaurine, while in (+)-thalicarpine and its analogues, coupling is instead with a (+)-reticuline unit. No proaporphine-benzylisoquinoline is involved in the biogenesis of these dimeric alkaloids. This stands in contrast to the dimeric aporphine benzylisoquinolines found in the Berberidaceae, such as pakistanine and khyberine. These alkaloids are derived from the condensation of two *N*-methylcoclaurine units, and their biogenesis does proceed through proaporphine-benzylisoquinoline dimers.[7]

Very recently, two in vivo studies using labeled precursors have appeared in the literature in which it was firmly established that the 1,2,9,10-tetraoxygenated aporphines (+)-boldine and (+)-isoboldine are efficient precursors of (+)-thalicarpine (**3**).[8,9] These results furnish direct support for oxidative coupling between a benzylisoquinoline and an aporphine to supply an aporphine-benzylisoquinoline dimer.[10]

Acknowledgment. This research was supported by Grant CA-11450 from the National Cancer Institute, National Institutes of Health, USDHHS.

(5) NMR NOE values were obtained by the NOE difference technique, using a 360-MHz FT spectrometer.

(6) For a listing of aporphine-benzylisoquinoline dimers, see Guinaudeau, H.; Leboeuf, M.; Cavé, A. *J. Nat. Prod.* **1979**, *42*, 325.

(7) Guinaudeau, H.; Elango, V.; Shamma, M.; Fajardo, V. *Chem. Commun.* **1982**, 1122.

(8) Bhakuni, D. S.; Jain, S. *Tetrahedron* **1982**, *38*, 729.

(9) Sidjimov, A. K.; Marekov, N. L. *Phytochemistry* **1982**, *21*, 871.

(10) In ref 8 above, it was concluded that thalicarpine (**3**) is formed via a dienone-phenol intermediate. This conclusion is unwarranted and is not supported by the experimental findings.

(11) Four kilograms of the dried roots and rhizomes was extracted with cold ethanol. The chloroform-soluble alkaloidal fraction was chromatographed on Merck silica gel H for TLC, elution being with $CHCl_3$-MeOH-NH_4OH (90:10:0.2). Further purification was by TLC on Merck silica gel F-254 using the system CH_3CN-C_6H_6-EtOAc-MeOH-NH_4OH (40:30:20:5:5). Seventeen milligrams of uskudaramine was thus obtained.

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General Stereospecific Synthesis of Trisubstituted Alkenes via Stepwise Hydroboration

Summary: Iodination of alkenylalkylbromoboranes, obtained via the hydroboration of internal alkynes with alkylbromoboranes, in the presence of sodium methoxide in methanol, results in the formation of trisubstituted alkenes of established stereochemistry, thus providing a general synthesis of trisubstituted alkenes with unambiguous stereochemistry.

Sir: Synthesis of trisubstituted alkenes of defined stereochemistry is one of the important objectives of organic

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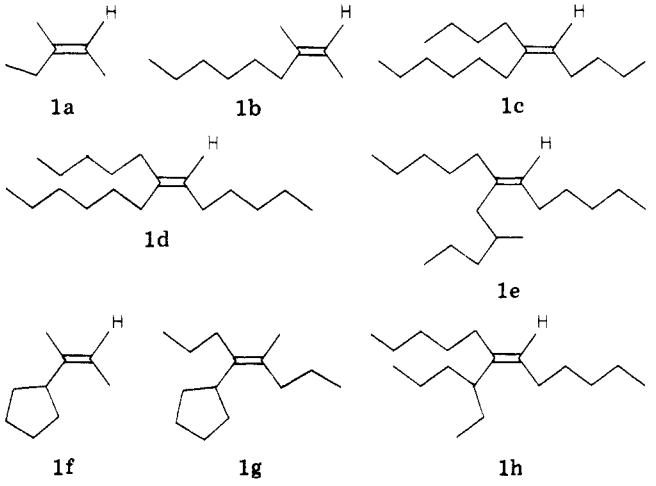
Table I. Synthesis of Trisubstituted Alkenes from Alkyldibromoborane and Internal Alkynes[a]

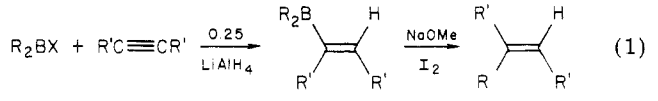
alkene for $RBBr_2 \cdot SMe_2$	alkyne	product[b]	yield,[c] %	bp, °C/mm	$n^{20}D$
ethylene	2-butyne	1a[d]	75[e]		
1-hexene	2-butyne	1b	71	62-63/15 mm (lit.[4] 64-65/16)	1.4280 (lit.[4] 1.4263)
1-hexene	5-decyne	1c	76	96-98/0.5	1.4447
1-hexene	6-dodecyne	1d	74	120-122/0.5	1.4479
2-methyl-1-pentene	6-dodecyne	1e	72	121-122/0.6	1.4499
cyclopentene	2-butyne	1f	71	72-74/50 (lit.[4] 83-85/90)	1.4575 (lit.[4] 1.4571)
cyclopentene	4-octyne	1g	75	68-70/0.6 (lit.[4] 70-71/1)	1.4629 (lit.[4] 1.4645)
(Z)-3-hexene	6-dodecyne	1h	72	116-118/0.5	1.4487

[a] All reactions were carried out in 30-mmol scale (except 1a). [b] Chemical purities of all products were >97% by GC analysis on a 6-ft SE-30 column; structures were confirmed by ^1H and ^{13}C NMR spectral data. [c] Yields of pure products, isolated by distillation, based on alkene or alkyne. [d] Reaction was carried out on 10-mmol scale. [e] GC yield determined with use of an internal standard; isomeric purity 100% by GC analysis on 12 ft × 0.25 in. 20% TCP on firebrick.

Chart I



chemists during recent years due to the widespread occurrence of these alkene units in many classes of naturally occurring, biologically active compounds.[1] Organoboranes have become increasingly important in the formation of carbon–carbon bonds.[2,3] Recently we reported[4] a general and stereospecific synthesis of trisubstituted alkenes (1) via the iodination of dialkylvinylboranes, obtained by the hydroboration of internal alkynes with dialkylboranes, in the presence of sodium methoxide (eq 1), thus generalizing the original Zweifel synthesis of trisubstituted alkenes.[5]

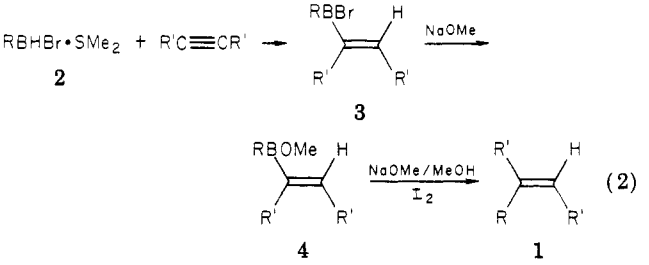


(1)

1

However, this procedure suffers from a significant disadvantage. One of the two alkyl groups on boron is not utilized, rendering this procedure undesirable in cases where the alkyl group is derived from an expensive alkene or difficulty synthesized alkene. Now we report a general synthesis of trisubstituted alkenes that avoids this difficulty.

Recently we reported[6] a general synthesis of Z-disubstituted alkenes via the iodination in the presence of sodium methoxide of alkenylalkylbromoborane, obtained via the hydroboration of 1-alkynes with alkylbromoboranes, $RBHBr \cdot SMe_2$ (2).[7] Consequently, it appeared to us that iodination of alkenylalkylbromoborane (3), obtained via the hydroboration of an internal alkyne with alkylbromoborane (2), in the presence of sodium methoxide should provide the desired trisubstituted alkene 1 with unambiguous stereochemistry (eq 2). Therefore, we undertook to examine this reaction sequence as a potential route for the synthesis of trisubstituted alkenes of established stereochemistry.



(2)

2 3 4 1

We first examined the hydroboration of internal alkynes with alkylbromoborane 2 and established that no dihydroboration occurs, thus providing a clean monohydroborated vinylborane 3.[8] Iodination of the vinylborane 3 was carried out in the presence of sodium methoxide in methanol at room temperature to provide the expected trisubstituted alkene 1 (eq 2). Representative alkenes (1a–h, Chart I) were prepared by using this reaction sequence (Table I).

The stereospecificity of this reaction was established by the synthesis of a simple trisubstituted alkene (2Z)-3-methyl-2-pentene (eq 3). Both E and Z isomers of 3-methyl-2-pentene are known[9a] and available.[9b] They

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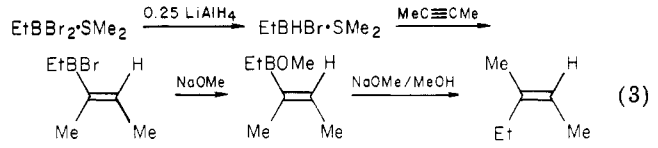
(8) In the present experiment about 5–10% of 4-octyne remained unreacted corresponding to the amount of ether-cleaved product $RB(OEt)_2$ formed during the hydridation step (estimated by ^{11}B NMR spectrum of 2), indicating that there is no dihydroboration. For experimental details, see: Brown, H. C.; Basavaiah, D.; Kulkarni, S. U. *J. Organometal. Chem.* **1982**, *225*, 63.

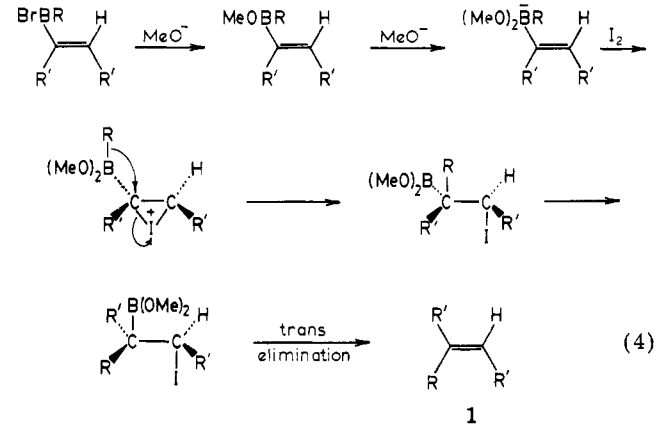
(9) (a) Prepared and characterized: Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. (b) Available from Wiley Organic, Inc.



(3)

separate nicely on a 12 ft × 0.25 in. column packed with 20% tricresyl phosphate on firebrick (60–80 mesh). The alkene, obtained via the reaction in eq 3, proved identical with the *Z* isomer, with no detectable amount of the *E* isomer.

The ^{13}C NMR spectra of (*E*)- and (*Z*)-3-methyl-2-pentenes are distinctly different. We found that the higher alkenes, obtained via the reaction sequence in eq 2, did not indicate the presence of more than one isomer in the ^{13}C NMR spectrum or on the tricresyl phosphate column. Consequently, we conclude that these higher alkenes should have the same stereochemistry as that of (2*Z*)-3-methyl-2-pentene. These results also clearly show that a mechanism similar to that involved in the formation of *Z*-disubstituted alkenes is operative. The migration of the alkyl group proceeds with inversion at the migration terminus and deiodoboronation occurs in a trans manner, thus resulting in the trans stereochemistry of the two alkyl groups from the internal alkyne (eq 4).



(4)

1

The following procedure for the synthesis of (6*Z*)-7-*n*-pentyl-6-tridecene (**1d**) is representative. To 30 mmol of *n*-hexyldibromoborane–dimethyl sulfide,[10] prepared from 1-hexene and dibromoborane–dimethyl sulfide, were added at 0 °C 3 mL of SMe_2 and 25 mL of Et_2O, followed by a slow addition of $LiAlH_4$ in Et_2O (7.5 mmol) with stirring under nitrogen. The reaction was allowed to proceed 3 h at 0 °C and 1 h at room temperature. The resulting alkylbromoborane was slowly transferred to a solution of 6-dodecyne (4.99 g, 30 mmol) in Et_2O at 0 °C and the reaction mixture was stirred 0.5 h at 0 °C and 1.5 h at room temperature. Then the resulting vinylborane was added slowly to a solution of NaOMe (150 mmol) in MeOH at 0 °C. After 0.5 h at room temperature, the solvent ether was removed under vacuum and 30 mL of MeOH was added. Iodine (7.60 g, 30 mmol) was added to this vinylborane solution in MeOH at 0 °C and the mixture was stirred at room temperature for 3 h. Aqueous $Na_2S_2O_3$ solution was added and the reaction mixture was extracted with pentane and the extract dried over anhydrous $MgSO_4$. Solvent was removed under reduced pressure and distillation afforded 5.6 g (74%) of (6*Z*)-7-*n*-pentyl-6-tridecene (**1d**): bp 120–122 °C (0.5 mm); n^{20}_D 1.4479. GC analysis showed 99% chemical purity; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.70–1.66 (m, 29 H), 1.73–2.26 (m, 6 H), 5.00 (t, *J* = 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.60, 22.41, 27.46, 27.78, 28.25, 29.25, 29.69, 31.46, 31.68, 39.69 (alkyl C), 124.61, 138.73 (C=C). For the assignment of stereochemistry (2*Z*)-3-methyl-2-pentene (**1a**) was prepared from $EtBBr_2{\cdot}SMe_2$[11] and 2-butyne following this procedure.

This procedure circumvents the significant problem associated with the earlier procedure,[4] thus providing a general one-pot and stereospecific synthesis of trisubstituted alkenes under mild conditions. However, it needs to be pointed out that this procedure has a significant limitation. This method is mainly applicable to symmetrical alkynes as the hydroboration of unsymmetrical alkynes is not completely regioselective. We are now exploring the possibilities of surmounting this limitation to provide a general and stereospecific synthesis of trisubstituted alkenes with all three groups different.

(10) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1980**, *45*, 384.

(11) $EtBBr_2$ was prepared via redistribution of Et_3B and BBr_3 catalyzed by $BH_3{\cdot}SMe_2$ (7–10%) in pentane at room temperature [$EtBBr_2{\cdot}SMe_2$, bp 112–114 °C (15 mm)]: Brown, H. C.; Basavaiah, D.; Bhat, N. G., manuscript in preparation.

(12) Postdoctoral research associate on Grant GM 10937-19 from the National Institutes of Health.

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Observations on the Mechanism of the Lewis Acid Catalyzed Ene Reaction

Summary: The product resulting from the $SnCl_4$-catalyzed reaction of allylbenzene and diethyl mesoxalate is shown to be an oxetane, contrary to the tetrahydrofuran structure assigned by previous authors.[4] This evidence, taken together with the evidence of a β-secondary deuterium isotope effect in the $SnCl_4$-catalyzed reaction, supports a mechanism of rate-limiting complex formation, in contrast to the corresponding purely thermal superene[2,3] reaction where the rate-determining step has been previously shown to involve pseudopericyclic H transfer in a rapidly formed (2 + 2) charge-transfer intermediate.

Sir: Through measurements of the temperature dependence of the kinetic isotope effect (TDKIE)[1] in the ene reactions of certain heteroatom multiple bonds,[2] which could be classified as superenophiles,[3] it has been shown that H transfer effected by purely thermal means takes place angularly, i.e., in a bent transition state (TS). Studies of the secondary D-isotope effects at the ene centers,[2b] as well as the regio- and stereoselectivity[2,3] associated with the ene reaction mechanism, have enforced the conclusion that in such cases a rapidly reversible (2 + 2) charge-transfer (CT) complex is formed between the ene and

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