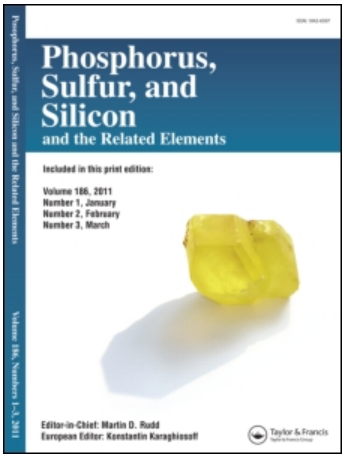

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NEW RADIOHALOGENATED ALKENYL TELLURIUM FATTY ACIDS

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NEW RADIOHALOGENATED ALKENYL TELLURIUM FATTY ACIDS

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Abstract Radiolabeled long-chain fatty acids have diagnostic value as radiopharmaceutical tools in myocardial imaging. Some applications of these fatty acids are limited due to their natural metabolic degradation in vivo with subsequent washout of the radioactivity from the myocardium. The identification of structural features which will increase the myocardial residence time without decreasing the heart uptake of long-chain fatty acids is of interest. Fatty acids containing the tellurium heteroatom were the first modified fatty acids developed and show unique prolonged myocardial retention and low blood levels. Our detailed studies with radioiodinated vinyliodide substituted tellurium fatty acids demonstrate that heart uptake is a function of the tellurium position. New techniques of tellurium and organoborane chemistry have been developed for the synthesis of a variety of radioiodinated iodoalkenyl tellurium fatty acids.

INTRODUCTION

The introduction of the tellurium heteroatom (Te) in the fatty acid is a unique strategy devised to inhibit β-oxidation and "trap" the fatty acid in the myocardium.[1] The Te fatty acids were the first examples of modified fatty acids in which catabolism is inhibited resulting in significantly prolonged heart retention. Such retention is required for the state-of-the-art single photon computerized tomographic (SPECT) imaging methods used in nuclear medicine to evaluate the regional distribution of radiopharmaceuticals in the heart. Tellurium can be readily incorporated while maintaining the linearity of the fatty acid molecules. Tellurium-123m-labeled 9-tellura-heptadecanoic acid (9-THDA) shows rapid and pronounced

myocardial uptake in rats[2] and dogs.[3,4] The unique properties of 9-THDA and related tellurium-substituted fatty acids are the prolonged myocardial retention and high heart:blood ratios.

To take advantage of the more attractive radionuclidic and chemical properties of the iodine-123 radioisotope (13.3 h half-life) in comparison to tellurium-123 (119 d half-life), the development of radioiodinated fatty acids containing stable tellurium has been explored. We have pursued a variety of synthetic strategies[1-7] for the introduction of tellurium into the fatty acid chain and radiohalogen as a terminal vinyl iodide. We have now prepared for the first time a series of Te fatty acids containing the internal alkenyl iodide moiety.

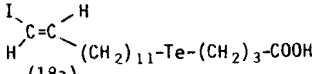
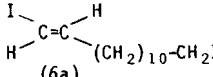
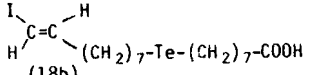
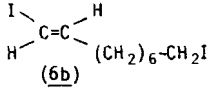
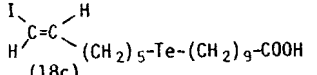
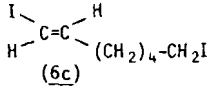
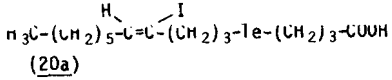
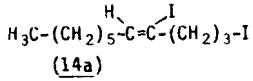
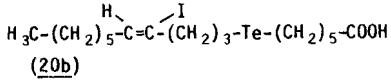
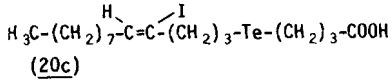
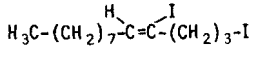
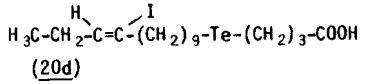
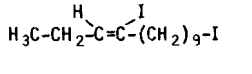
Iodoalkyl-substituted tellurium fatty acids such as 17-iodo-9-telluraheptadecanoic acid have been prepared by a simple route involving halogen exchange of 17-bromo-9-telluraheptadecanoic acid (BTHDA).[8] A study of the tissue distribution of radioactivity of BTHDA in rats showed accumulation of radioactivity in the thyroid indicating in vivo deiodination of this agent. Methods have been developed to introduce radioiodine as an alkenyl iodide moiety in the fatty acids to inhibit in vivo deiodination.

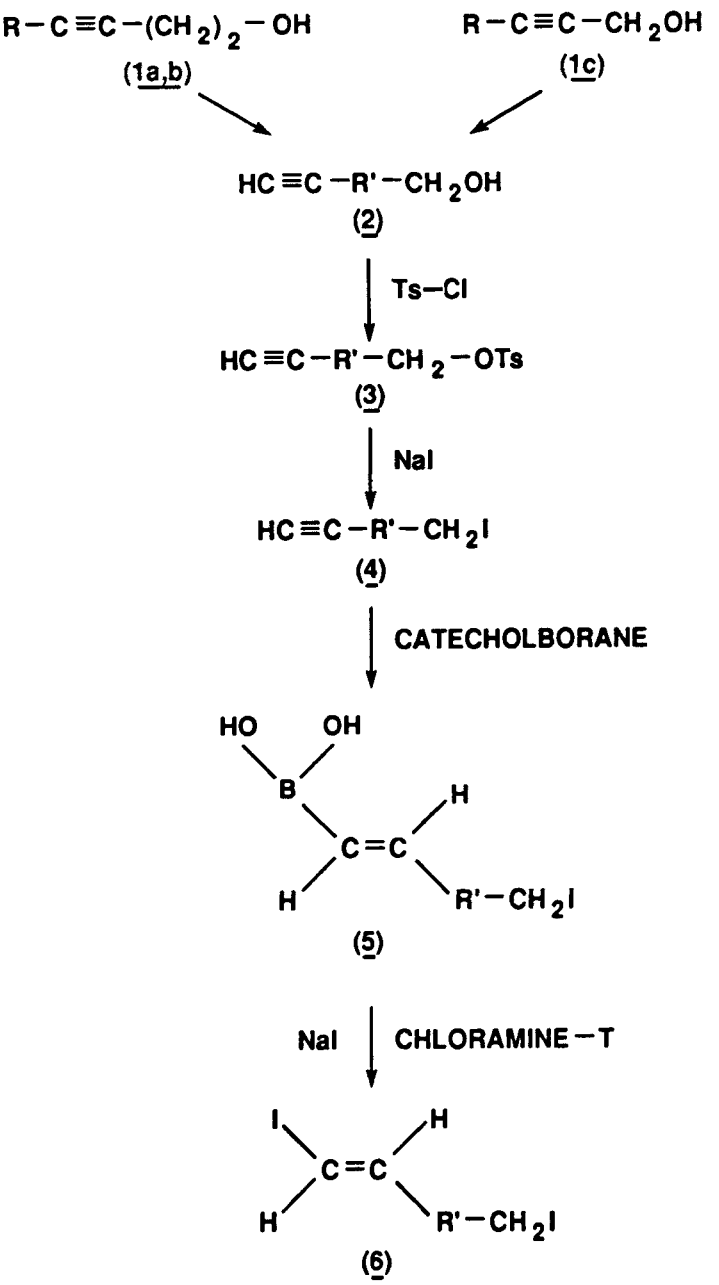
Kabalka, Sastry and Somayaj[9] showed that vinyl iodides can be readily prepared via the sodium iodide-chloramine-T treatment of the corresponding boronic acids. This reaction greatly facilitated the synthesis of a variety of iodovinylalkyl iodides as precursors for the synthesis of radioiodinated tellurium fatty acids. A general route for the synthesis of iodovinylalkyl iodides was developed earlier as shown in Scheme I. Several agents have been prepared by this strategy (a-c, Table 1, Scheme I).

SYNTHESIS OF NEW ALKENYL TELLURIUM FATTY ACIDS

In order to evaluate the effects of Te position and the

Table 1. Precursors used for the synthesis of tellurium fatty acids.

Fatty acid	Diiodoalkene substrate	Ditelluride substrate
 (18a)	 (6a)	$[-Te-(CH_2)_3-COOEt]_2$ (15a)
 (18b)	 (6b)	$[-Te-(CH_2)_7-COOMe]_2$ (15b)
 (18c)	 (6c)	$[-Te-(CH_2)_9-COOMe]_2$ (15c)
 (20a)	 (14a)	(15a)
 (20b)	(14a)	$[-Te-(CH_2)_5-COOMe]$
 (20c)		(15a)
 (20d)		(15a)



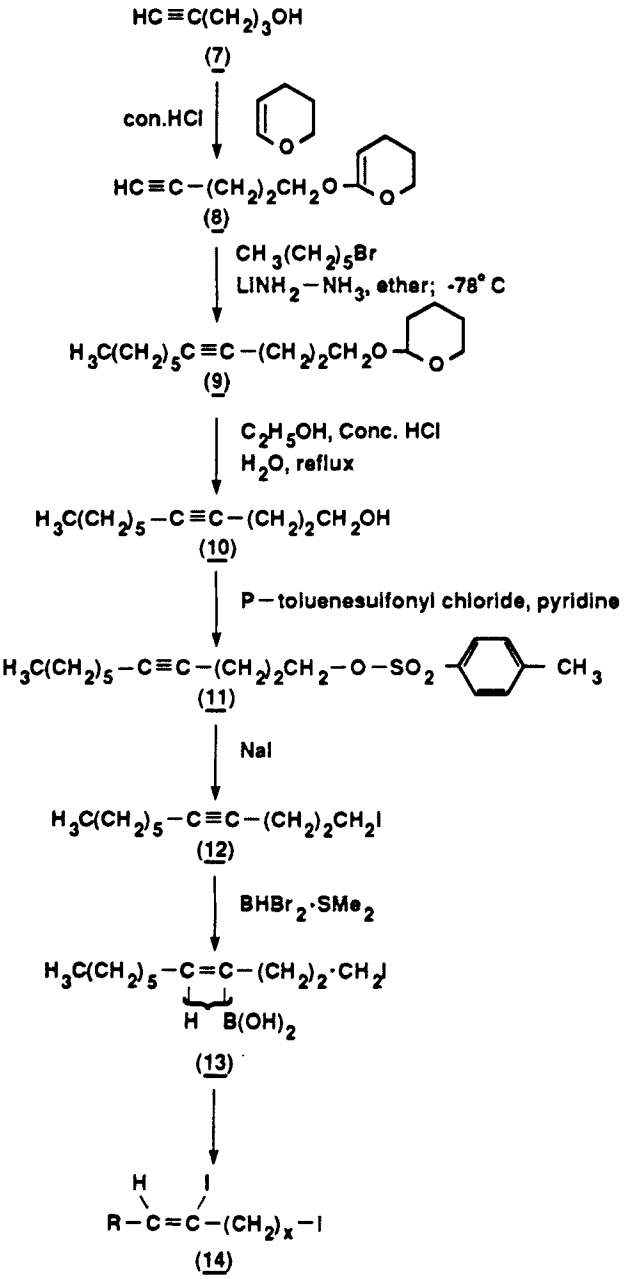
Scheme 1

introduction of iodine as an internal alkenyliodide, we have now prepared for the first time a series of internal alkenyliodide Te fatty acids. The general procedure for the preparation of internal alkenyl iodides (Scheme II) involves protection of the hydroxyl group of a terminal acetylenic alcohol (7) by reaction with dihydropyran with subsequent coupling with the requisite alkyl bromide to form the internal alkyne (9). Following acid cleavage of tetrahydropyranyl ether (9), the free alcohol (10), was converted to the tosylate (11). The tosylate (11) was converted to the iodide (12) by treatment with KI and iodide then converted to the isomeric (4,5) mixture of the internal alkenyl boronic acid (13). In this way a series of substrates was prepared and iodinated using sodium iodide and chloramine-T to yield isomeric mixture of diiodoalkenes 14 (a-d, Table 1, Scheme II).

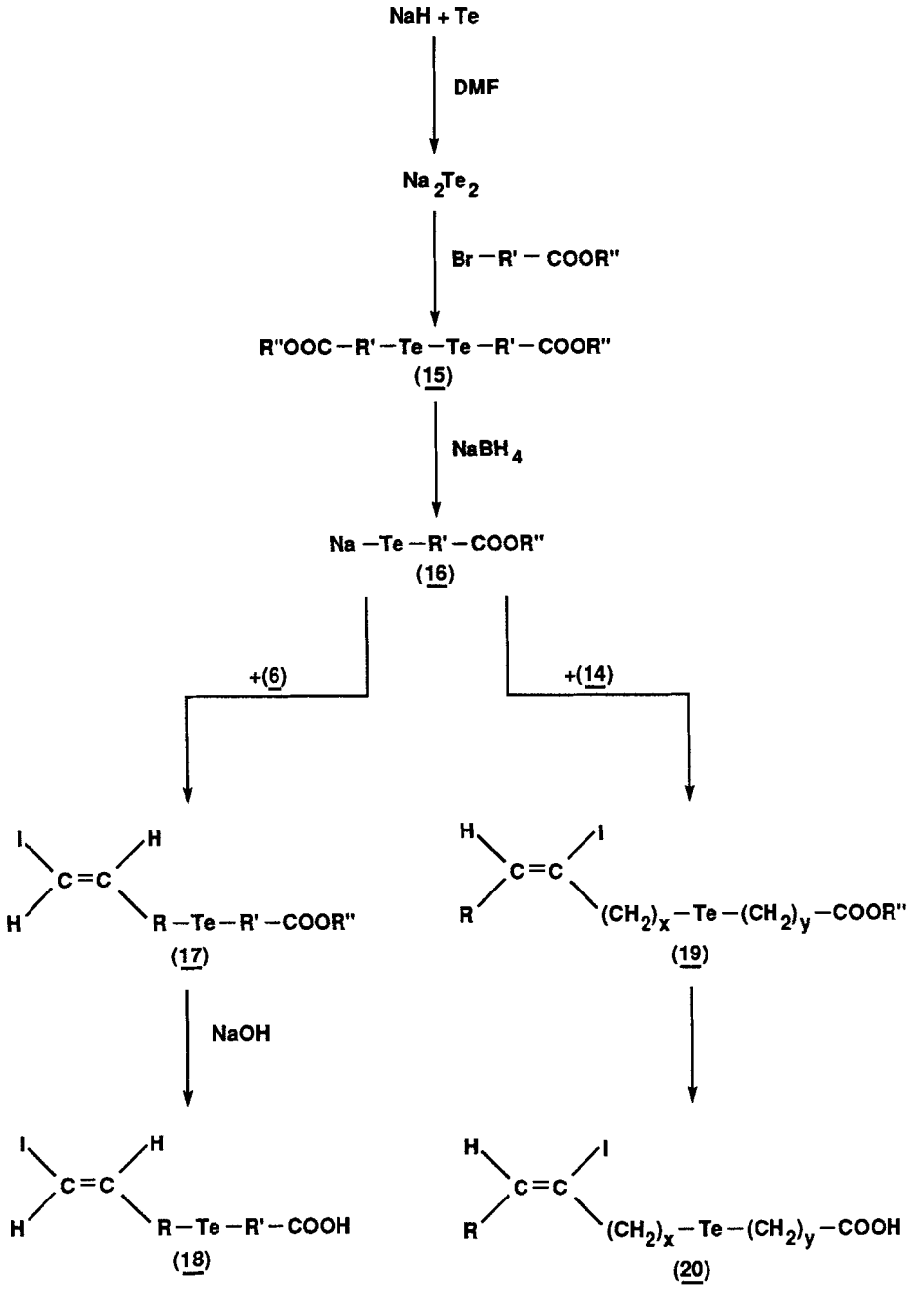
The diiodoalkenes (6 and 14) were coupled with the requisite sodium (alkoxycarbonyl)alkyl telluride substrates (16, Scheme III), to provide the tellurium fatty acid esters (17 and 19). The tellurides (16) were generated by in situ $NaBH_4$ reduction of the dialkyl ditelluraalkanedioates (15), which were prepared by alkylation of Na_2Te_2 with alkoxycarbonyl-ω-bromoalkanes. The fatty acid esters were obtained after purification (silica gel column chromatography) and converted to free fatty acids (18 and 20) by basic hydrolysis using 1 N sodium hydroxide in boiling ethanol. The details of the preparation of these analogues are summarized in Table 1 and Scheme III.

BIOLOGICAL STUDIES

Tissue distribution studies were performed using ^{125}I-labeled tellurium fatty acids which were prepared by $Na^{125}I$ conversion of boronic acids, followed by coupling with the sodium tellurol and hydrolysis with base. The ^{125}I-labeled fatty acids were



Scheme 2



Scheme 3

Table 2. Distribution of radioactivity in tissues of Fischer 344 female rats following intravenous administration of E-[^{125}I]iodoalkenyl tellurium fatty acid analogues.

Fatty acid	minutes after injection	Mean percent injected dose/gm Tissue						Mean H:B ratio
		Heart (H)	Blood (B)	Liver	Lungs	Kidneys	Thyroid	
18a	5	3.99	0.11	6.56	1.47	1.02	6.03	37
	30	4.64	0.16	5.53	1.54	1.02	11.6	30
	60	4.33	0.19	7.33	1.16	1.16	14.1	23
18b	5	4.83	0.23	6.41	1.63	1.58	9.21	21
	30	3.76	0.45	5.69	1.52	1.38	15.0	8
	60	5.17	0.36	4.87	1.57	1.52	24.8	14
18c	5	3.09	0.45	8.33	2.49	2.22	29.0	7
	30	3.05	0.66	6.49	2.06	1.85	29.0	5
	60	3.63	0.67	5.15	2.07	1.92	37.0	5
20a	5	5.11	0.33	14.23	0.67	...	10.44	15.5
	30	5.76	0.48	11.51	0.57	...	17.19	12.0
	60	6.52	0.32	9.24	0.50	...	28.78	20.4
20b	5	4.17	0.65	15.6	2.29	2.41	10.3	6.4
	30	4.76	0.67	12.1	1.95	2.41	11.7	7.1
	60	5.66	0.49	9.3	1.84	2.23	13.9	11.2
20c	5	2.07	1.66	9.83	2.45	2.47	21.8	1.3
	30	1.11	1.20	5.12	1.14	2.17	65.5	0.9
	60	0.66	0.89	3.39	0.78	1.26	118.0	0.7
20d	5	2.83	1.02	10.08	2.89	2.14	14.2	2.8
	30	1.39	0.95	5.35	1.22	2.15	47.8	1.5
	60	0.80	0.82	4.39	0.84	1.67	69.7	0.9

complexed with bovine serum albumin and injected intravenously into female Fischer rats.[5] The tissue distribution data after different time intervals are summarized in Table 2.[5] A dramatic relationship is seen between heart uptake, myocardial retention heart/blood ratios and the position of Te heteroatom.

CONCLUSION

The data from these studies have demonstrated the dramatic effect of tellurium position on the heart uptake of iodovinyl-tellurium fatty acids (18a-18c), among which the 5-tellura analogue 18a shows the highest myocardial uptake. However, the results obtained from internal alkenyl tellurium fatty acids (20a-20d) demonstrate an unexpected relationship between fatty acid structure and myocardial uptake and clearance properties. Although the factors effecting the in vivo properties are not clear, these studies have shown that a combination of chain length, Te position and the relative position of the internal iodoalkenyl substitution are important factors. The most interesting result is the clearance of analogues 20c and 20d which has not been demonstrated with other analogues.

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