A convergent approach to (*R*)-Tiagabine by a regio- and stereocontrolled hydroiodination of alkynes†

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The occurrence of unsaturated systems in natural products combined with the mildness and the wide range of applicability of $CeCl_3$ promoted methodologies suggest several potential future synthetic applications within the field of total synthesis of biologically active molecules. On this concept, the use of $CeCl_3 \cdot 7H_2O$–NaI system as an efficient heterogeneous promoter has been highlighted in the iodofunctionalization of carbon–carbon triple bonds. The study has shown that this method would be particularly interesting for the stereoselective formation of trisubstituted (*Z*)- or (*E*)-iodoalkenes by simply changing the nature of the solvent. The methodology has been successfully applied to the synthesis of (*R*)-1-[4,4-bis-(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid **1**, named (*R*)-Tiagabine, which is a potent and selective γ-aminobutyric acid (GABA) uptake inhibitor with proven anticonvulsant efficacy in humans.

Introduction

Trisubstituted alkenes have been and continue to be highly significant organic compounds with biological activity. A large number of compounds having biological and pharmaceutical activity incorporate this moiety, and a plethora of methods for the synthesis of this valuable fragment is known in organic chemistry.[1] Recent years have witnessed the wide development of palladium catalyzed C(sp^2)–carbon bond-forming reactions, in large part due to typically mild reaction conditions, the ease of preparation of a wide range of coupling partners, and the tolerance of a wide variety of sensitive functionalities in this transformation.[2] In particular, the Pd-catalyzed coupling processes of alkenyl halides and related compounds have become a central tool for the synthesis of biologically active compounds both in academia and industry.[3] Today, the Pd-catalyzed cross-coupling reactions of boronic acids with organic halides, known as Suzuki–Miyaura couplings,[4] may be frequently applied in the industrial manufacture of fine chemicals and pharmaceuticals.[5] One of the most remarkable applications of the Suzuki reaction in biological active products synthesis is found in the synthesis of polytoxin by Kishi and coworkers.[6] In continuation of the work of some of us on the synthesis of molecule targets with biological activity,[7] we report herein a demonstration of the utility of the Suzuki reaction by a simple and convergent synthetic approach for (*R*)-1-[4,4-bis-(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid (**1**).

Compound **1**, named (*R*)-Tiagabine (Fig. 1), is a GABA uptake inhibitor marketed for the treatment of epilepsy.[8] It is known that thiophene derivatives show numerous biological activities[9] and are of potential pharmacological significance,[10] consequently our attention was focused on a convergent synthesis of **1**. Furthermore, a series of cyclic amino acids and their derivatives which have diheteroaryl vinyl functions such as (*R*)-Tiagabine, have been found to inhibit key functional components of γ-amino butyric acid (GABA) in the mammalian central nervous system (CNS).[11] The observations of using these compounds as the basis for the design of new centrally-acting drugs have also stimulated investigations of their synthesis.[12] The overall strategy used for the preparation of the 4,4-diaryl/diheteroaryl butenyl structural class shows the major limitation in using hard conditions and reagents that are expensive and sensitive to air.[13] In order to further research on the biological activities of Tiagabine analogues, a new and more practical synthetic route would be useful.

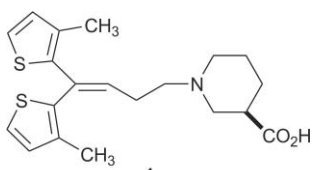

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Fig. 1 Structure of (*R*)-Tiagabine.

In the present work, not only a robust linear approach allowing exclusive formation of the desired (*R*)-Tiagabine (**1**) has been described, but also the ability of $CeCl_3 \cdot 7H_2O$ to promote the regio- and diastereoselective addition to carbon–carbon triple bonds by selective coordination to π-electrons of alkynes for obtaining multifunctionalized trisubstituted alkenes.

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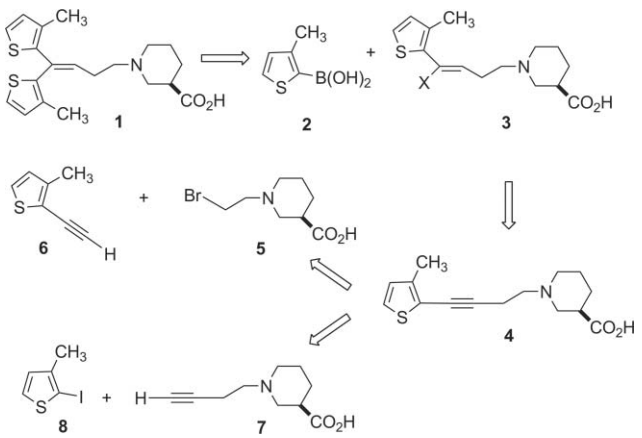
Results and discussion

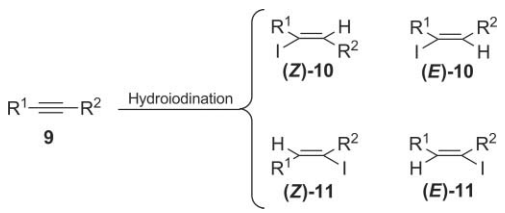
A very broadly applicable strategy for the preparation of trisubstituted alkenes in a stereoselective manner involves alkynes as a valuable functional group.[14] The stereoselective transformations of alkynes for the preparation of functionalized alkenes have emerged as powerful synthetic tools,[15] thus, we have thought to the functionalization of carbon–carbon triple bonds for installing the dithienylvinyl moiety in the molecule target **1**.

Retrosynthetic analysis reveals a route based on a convergent approach as outlined in Scheme 1. We have devised that the alkenyl thiophene derivative **3**, the key compound for the Suzuki coupling, could be introduced by hydrofunctionalization of alkyne **4**. The alkenyl triflates (X = OTf in compound **3**) have been found to be superior to alkenyl halides,[16] but they are rather expensive and their uses especially for the large-scale synthetic operation may not be economical. Thus, in the cases of vinyl moieties, iodides, and a lesser extension bromides, are commonly employed in the Suzuki reaction. Alkenyl chlorides are known to be less reactive than iodides or bromides, due to their slow oxidative addition to palladium.[17] Given that alkenyl iodides are generally more desirable that their bromo or chloro analogs,[18] there are a large number of methods developed for hydroiodination of alkynes and chemists continue to find ways to improve it.



Scheme 1 Retrosynthesis of (*R*)-Tiagabine (**1**).

In general, the direct conversion of substituted alkynes into the desired alkenyl iodides by hydroiodination (Scheme 2) with hydrogen iodide appears to be the most convenient method, but often leads to low yields, and side reactions due to uncontrollable iodine liberation.[19] More convenient is the sequential reaction of hydrometalation of various metal hydrides such as Schwartz's reagent to alkynes followed by demetalation with iodine.[20] Mildness of the reaction conditions makes it useful to prepare 1-iodo-1-alkenes (R^1 = H in **10**) in an anti-Markovnikov fashion.[21] However,



Scheme 2 Hydroiodination reaction of alkynes.

internal alkenyl iodides are scarcely obtained and difficulties in handling vinyl-metal species detract from the utility of this method.[22] Hydroiodination *via in situ* generation of hydrogen iodide has also been reported.[23] This strategy uses expensive reagents and harsh conditions, and only gives satisfactory results when starting from symmetric internal alkynes ($R^1 = R^2$ in **9**). Accordingly, these drawbacks have stimulated the search for better catalysts that could be superior to the existing ones with regard to selectivity and handling of reagents.

Studies by us and by others have resulted in the development of methodologies involving the $CeCl_3 \cdot 7H_2O$–NaI system for providing new means for promoting organic transformations in a variety of systems.[24] The commercially available reagents such as $CeCl_3 \cdot 7H_2O$ and NaI can be used in combination without any special caution.[25] The $CeCl_3 \cdot 7H_2O$–NaI system acts as a Lewis acid that activates multiple bonds *via* π-binding and the new bond-forming reactions proceed through an interaction between Ce(III) and C–C multiple bond.[26] Recently, Silveira and coworkers have reported the first methodology of hydrochalcogenation of terminal alkynes promoted by $CeCl_3$.[27] In the light of this background that we have studied a convenient procedure for transforming alkynes **9** into the corresponding alkenyl iodides**10** using the $CeCl_3 \cdot 7H_2O$–NaI system.

The treatment of phenylacetylene (**9a**) with 1.0 molar equiv of the $CeCl_3 \cdot 7H_2O$–NaI system in acetonitrile was inefficient at room temperature and moderate conversion into alkenyl iodide **10a** was obtained at reflux temperature. The results are summarized in Table 1. By screening the various conditions we have observed that the amounts optimized of $CeCl_3 \cdot 7H_2O$ and NaI used in the reaction request a molar ratio of alkyne **9a**, $CeCl_3 \cdot 7H_2O$, and NaI equal to 1 : 1.5 : 3. The use of a large excess of the $CeCl_3 \cdot 7H_2O$–NaI system afforded the alkenyl iodide adduct in significantly lower yield. Analogously, with a reduction of the amount of $CeCl_3 \cdot 7H_2O$–NaI the process becomes slower and the hydroiodination is not complete even after prolonged reaction times. A variety of solvents[29] were investigated and the efficiency based on the reaction conversion of **9a** and yields of **10a** is CH_3CN > toluene ≫ CH_2Cl_2 > THF > EtOH > DMF. In the case of AcOEt as a more inexpensive and environmental benign solvent than CH_3CN, our procedure gave, contrary to the resulted reported in literature,[30] a very low yield of adduct, and many side products were formed. The procedure in acetonitrile is not accompanied by small amounts of the hydrolysis product,[31] and with almost exclusive regiocontrol nucleophilic attack on the more substituted carbon atom. The presence of $CeCl_3 \cdot 7H_2O$ has been found to be essential for the reaction, because when the same reaction was carried out in the absence of $CeCl_3 \cdot 7H_2O$ no hydroiodination took place.

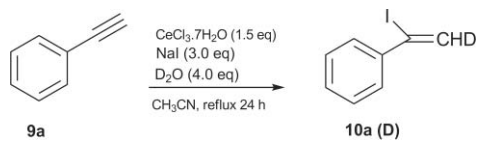
Having established what appeared to be the promoting pathway of the solid $CeCl_3 \cdot 7H_2O$, we switched our attention to the water of crystallization in the cerium(III) salt. The selection of hydrated Ce(III) salt plays a crucial role in the ability of the system to promote region- and stereoselective hydroiodination of alkynes, and it seemed appropriate to investigate the source of the vinyl hydrogen in our reaction. In fact, the reaction of **9a** works only in the presence of hydrated $CeCl_3$, while with dry $CeCl_3$[32] in dry acetonitrile no hydroiodination product **10a** was detected. When the reaction was repeated with <1 equiv of water,[33] decreased activity was observed and the alkenyl iodide **10a** was obtained in a yield less than 60%. In addition, with 4 equiv of water,

Table 1 Hydroiodination of alkynes **9a–l** by $CeCl_3 \cdot 7H_2O$ (1.5 eq) and NaI (3.0 eq) in CH_3CN under reflux conditions

Entry[a]	R^1	R^2	Alkyne	Time/h	Yield (%)[b]	Alkenyl Iodide[c]		Z/E[d]
1	C_6H_5	H	**9a**	24	90	**10a**	—	
2	2-$CH_3C_6H_4$	H	**9b**	20	95	**10b**	—	
3	2-$CH_3OC_6H_4$	H	**9c**	14	95	**10c**	—	
4	4-BrC_6H_4	H	**9d**	30	82	**10d**	—	
5	4-$CF_3C_6H_4$	H	**9e**	45	75	**10e**	—	
6	$C_6H_5CH_2CH_2$	H	**9f**	24	90	**10f**	—	
7[e]	C_6H_5	CH_3	**9g**	24	90	**10g**	**11g**	95 : 05
8[f]	C_6H_5	CH_3	**9g**	24	55	**10g**	**11g**	20 : 80
9	C_6H_5	$CH(CH_3)_2$	**9h**	24	82	**10h**	**11h**	92 : 08
10[f]	C_6H_5	$CH(CH_3)_2$	**9h**	24	79	**10h**	**11h**	16 : 84
11	H	$COOCH_3$	**9i**	14	93	**10i**	—	99 : 01
12	C_6H_5	$COCH_3$	**9j**	16	84	**10j**	**11j**	96 : 04
13[f]	C_6H_5	$COCH_3$	**9j**	16	82	**10j**	**11j**	11 : 89
14	CH_3	CH_2OH	**9k**	24	mixture of products[28]			
15[e]	CH_3	CH_2OCOPh	**9l**	24	79	**10l**	**11l**	99 : 01
16[f]	CH_3	CH_2OCOPh	**9l**	24	57	**10l**	**11l**	99 : 01

[a] All reactions were carried out by stirring mixtures of alkyne **9** and $CeCl_3 \cdot 7H_2O$–NaI system in acetonitrile (10 mL $mmol^{-1}$ of alkyne) for the selected reaction times. [b] Yields of products isolated by flash chromatography. [c] All products were identified by their IR, NMR, and GC-MS spectra. [d] Calculated *Z*/*E* ratio on the mixture of diastereomers isolated by column chromatography. [e] Regiosomer ratio by NMR: **10g** : **11g** (90 : 10 in acetonitrile and 97 : 03 in toluene); **10l** : **11l** (92 : 08 in acetonitrile and 85 : 15 in toluene). [f] The reaction was carried out in the same conditions but using toluene as solvent.

essentially identical results were obtained as with the cerium salt heptahydrate. Thus, in our hydroiodination reaction which gave (*Z*)-alkenyl iodides, the iodine and the vinyl hydrogen add to the alkyne in a *trans*-fashion and the vinyl hydrogen comes from the hydroxyl group of water. To obtain further evidence to confirm the source of the vinyl hydrogen in our reaction, we have carried out the reaction by using dry $CeCl_3$ and adding D_2O instead of H_2O.[34] By NMR and MS techniques after quenching of the reaction mixture we observed deuterium incorporation at vinyl-position (Scheme 3). This deuteration experiment would strongly support the effective participation by the water as the source of the vinyl hydrogen.



Scheme 3 Deuteration experiment with **9a**.

It should be to noted that the mixture might at the end just form HI *in situ*, but in the presence of a strongly hindered base such as 2,6-di-*tert*-butyl-4-methylpyridine, which only binds to HI without deactivating the $CeCl_3 \cdot 7H_2O$–NaI system,[35] the methodology has afforded alkenyl iodides **10** in high yield and with absolutely purity. This investigation aimed at confirming the exception of a Brønsted acid pathway in our procedure. Thus, not only does our Lewis acid system perform best in the presence of water,[36] but also its promoting activity is amplified by the water. This effect is taken as a proof-of-principle that substrate interaction cerium(III) Lewis acid species and water are not mutually exclusive.[37] Finally, different Lewis acids proved to be less effective affording the corresponding alkenyl iodide product in lower yield (Table 2).[38]

The methodology tolerates alkyl-, aryl- and heteroaryl-substituents on the alkyne moiety, and in the case of internal alkynes (R^1 and $R^2 \neq H$) the hydroiodination proceeds in a highly strereoselective manner,[39] with the preferential formation

Table 2 Hydroiodination of **9a** promoted by various hydrated Lewis acids[a]

Lewis acid	Yield (%)[b]	Lewis acid	Yield (%)[b]
$CeCl_3 \cdot 7H_2O$	90	$InBr_3$	33
$CeBr_3$	60	$Yb(OTf)_3$	40
CeI_3[c]	64	$LaCl_3 \cdot 7H_2O$	45
$Ce(OTf)_3$	47	$La(NO_3)_3 \cdot 6H_2O$	38
$InCl_3$	25	$TiCl_4$	Trace[d]

[a] Conditions: Lewis acid, substrate **9a**, and NaI were mixed in acetonitrile (10 mL $mmol^{-1}$ of alkyne **9a**), and stirred at reflux for 24 h. [b] Yields of products isolated. [c] CeI_3 is not able to promote hydroiodination in the absence of NaI. [d] Starting material was recovered after reaction.

of the thermodynamically more stable isomer (*Z*)-**10**. The stereochemistry was confirmed by NOESY-1D experiments,[40] which revealed key correlations between vinyl protons and protons in vinyl substituents as shown in Fig. 2. The selective formation of the (*Z*)-**10** isomer would require that the species $[H]^+$ and $[I]^-$ are donated by different molecules in a stepwise process. A possible reaction mechanism, depicted in Scheme 4, may involve the following steps: (*i*) coordination of the alkynyl moiety of **9** to the Ce(III) salt gives the complex **A**; (*ii*) the complex **A** may form an organocerium intermediate **B** or **C** by the nucleophilic attack of iodide anion; (*iii*) rapid protodemetalation,[41] by coordinated water molecules on the surface, which serve as hydrogen donors, affords products **10** with high diastereoselectivity. In a non polar solvent such as toluene (Table 1, entries 8, 10, and 13) transfer of iodide anion to the complex **A**, in competition with diffusion, occurs rapidly through *path a* and affords predominantly the *syn* addition products (*E*-configuration). In contrast, in polar solvents such as CH_3CN the solvation free energy stabilizes the separate ions and the change in mechanism may be due to a slower addition of iodide anion and subsequent formation of the thermodynamically more stable (*Z*)-isomers (*path b*).[42] As confirmation of this, noteworthy are the results 15 and 16 in Table 1 indicating the presence of an intramolecular coordination in the mixture of the two possible

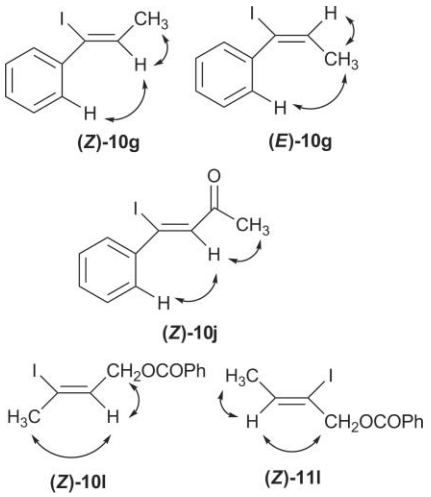
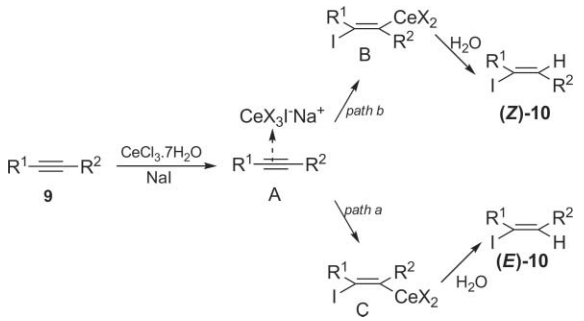


Fig. 2 Stereochemistry assigned by nOe studies.

regioisomers, and the corresponding vinyl iodide (*Z*)-**10l** was isolated in high selectivity, irrespective of the solvent (acetonitrile or toluene) chosen. Unfortunately, no *anti*-iodoceration species could be discerned from the ^{1}H NMR and ^{13}C NMR, due, very probably, to the presence of paramagnetic Ce(III) species.[43] However, preliminary study by employment of an online ESI-MS technique[44] in the positive ion mode, allowed us to suggest species that contain a cerium–carbon bond. A complete study on the mechanistic aspects of the activation of carbon–carbon triple bonds by Ce(III) salts that will provide experimental evidence for the formation of organocerium species, will be reported in due course.

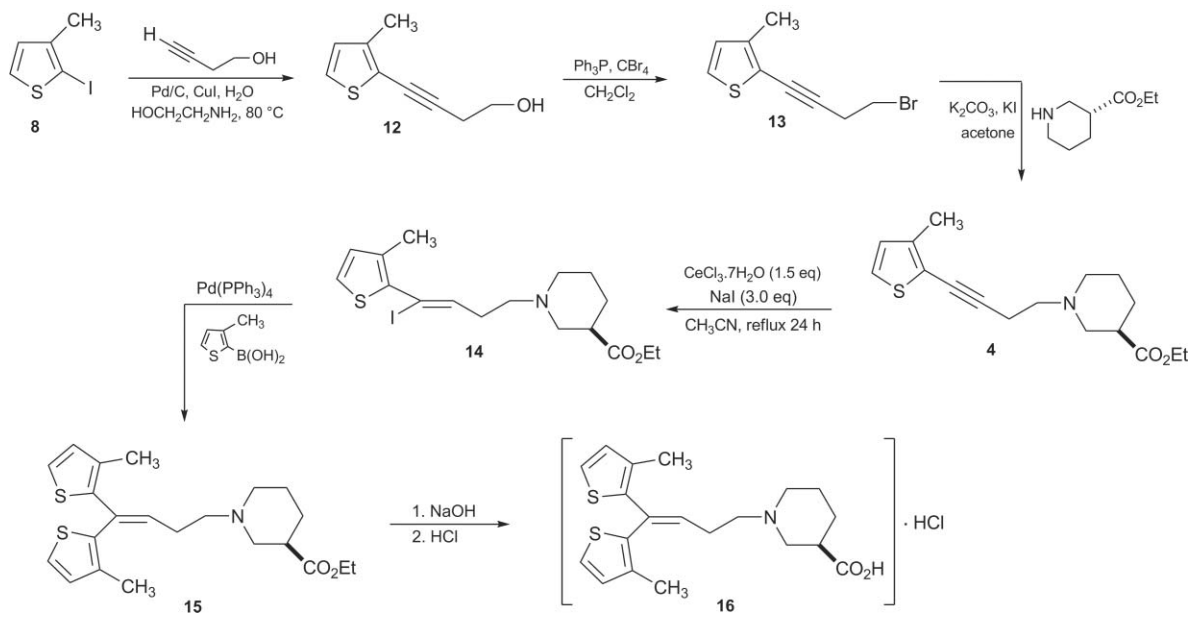
With an efficient procedure in hand for obtaining alkenyl iodide **3**, we decided to explore the synthetic application of alkyne **4**. The facility to obtain the bromide **5** by alkylation of the (*R*)-enantiomer of ethyl nipecotate under mildly basic conditions using 2-bromoethanol,[12c] suggested to us the Sonogashira coupling



Scheme 4 Proposed reaction mechanism.

reaction with terminal acetylene **6**. This intermediate was easily prepared by conversion of 3-methyl-2-thiophenecarboxaldehyde commercially available by the procedure of Corey and Fuchs[45] followed by treatment with n-butyllithium.[46] Unfortunately, it was found that in classical Sonogashira reaction conditions terminal acetylene **6** undergoes a homo-coupling reaction in the presence of a copper(I) halide catalyst, known as the Glaser reaction.[47] The homo-coupling product was the major product instead of the desired disubstituted product **4** even using ultrapure nitrogen as the protection gas. The use of hydrogen gas as a reducing reagent[48] or under copper-free Sonogashira reaction conditions[49] provide the desired product **4** in more than 15% yield as part of a complicated mixture. After numerous unsuccessful attempts, it sounds clear that this procedure would not be effective for alkyne **4**. Thus, we have thought to change synthetic strategy from C(sp)–C(sp^3) Sonogashira coupling reaction to C(sp^2)–C(sp) bond-forming reaction to avoid the homo-coupled byproduct.

Treatment of **8** (Scheme 5) with 3-butyn-1-ol in the presence of catalytic 10% Pd/C and CuI and ethanolamine in water at 80 °C afforded the 2-thienylbutynyl alcohol derivative **12** in good yield (Scheme 4). Subsequent bromination of the alcohol **12** with CBr_4 and PPh_3 furnished bromide **13** in 88% yield. Finally, The heteroaryl substituted compound **13**, after purification, reacted



Scheme 5 Convergent synthesis of (*R*)-Tiagabine.

with (*R*)-ethyl nipecotate to afford the ester **4**. In the key step, alkenyl iodide **14** was formed in 94% yield with 99% *Z*-selectivity by applying our procedure to alkynyl compound **4**. With the core unit in hand, the palladium-catalyzed Suzuki coupling with 3-methyl-2-thienylboronic acid gave the *N*-alkylated amino acid ester derivative **15**. Hydrolysis under basic conditions provided the free acid which was isolated as its crystalline hydrocholoride salt **16**, more stable than free-amine (with high optical and LC chromatography purity).

Conclusion

Following the convergent strategy as described in this work, it has been possible to synthesize diheteroalkenyl compounds, and in particular the strategy was efficiently applied for the preparation of (*R*)-Tiagabine (**1**). The strategy introduced herein has three key points which make it considerably more useful in comparison to the procedure reported so far: (*i*) the synthetic route is brief and conveniently produces the target compound from easily accessible starting materials, (*ii*) the desired biologically active trisubstituted alkenes were prepared by palladium-catalyzed coupling reactions without homo-coupled byproducts, and (*iii*) our procedure will be able to have the possibility of being used in the synthesis of diaryl vinyl functions with different aryl groups and to obtain molecules with an improved potency and pharmacological profile than (*R*)-Tiagabine.

With regard to the effectiveness of the $CeCl_3 \cdot 7H_2O$–NaI system in promoting organic transformations, the results obtained in this study support the important role that this Lewis acid plays in the synthesis of biologically active molecules. Our procedure of hydroiodination of substituted alkynes would be particularly interesting for the reason that it would allow the stereoselective formation of trisubstituted (*Z*)- or (*E*)-iodoalkenes by simply changing the polarity of the solvent. Further utilization of this flexible methodology in the synthesis of other biologically active compounds will be reported in due course.

Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ on Varian Gemini 200 or Varian 400 spectrometers and are reported as follows: chemical shift, δ (ppm) [number of protons, multiplicity, and coupling constant *J* (Hz)]. Residual protic solvent $CHCl_3$ ($\delta_H = 7.26$ ppm) was used as the internal reference. ^{13}C NMR spectra were recorded in $CDCl_3$ at 50 MHz or 100 MHz on Varian Gemini 200 or Varian 400 spectrometers, using the central resonance of $CDCl_3$ ($\delta_C = 77.0$ ppm) as the internal reference. The ^{13}C NMR peaks were assigned by standard methods using HMQC and DEPT experiments. *Z*/*E* Assignments were based on nOe studies. Mass spectra were recorded on a gas chromatography with a mass-selective detector, utilizing electron ionization (EI) at an ionizing energy of 70 eV or on a LC-MS utilizing an electrospray ionization (ESI) source. Microanalyses were performed with a EA1108 CHNS-D Fisons Instrument. Optical rotations were recorded on a polarimeter with a path length of 1 dm and are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g/100 mL. Melting points were determined in open capillary tubes on a Büchi 535 melting point apparatus and are uncorrected.

All air-sensitive reactions are carried out in flame dried glassware under an atmosphere of dry nitrogen. Solvents were distilled under nitrogen, tetrahydrofuran (THF) from sodium benzophenone ketyl and dichloromethane (CH_2Cl_2) from calcium hydride. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a Baker silica gel (230–400 mesh) column using ethyl acetate in hexane as the eluent. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F254) and visualized by UV light (254 nm) and/or by dipping the plates into Von's reagent (1.0 g of ceric sulfate and 24.0 g of ammonium molybdate in 31 mL of sulfuric acid and 470 mL of water).

General experimental procedure for alkenyl iodide synthesis

To a stirred suspension of alkyne **9a–l** (1 mmol) and sodium iodide (0.45 g, 3.0 mmol) in 15 mL of the appropriate solvent (Table 1) was added cerium(III) chloride heptahydrate (0.56 g, 1.5 mmol), and the resulting mixture was stirred at reflux until the disappearance of the starting alkyne. The reaction progress was monitored by withdrawing aliquots, which were analyzed by GC or TLC analysis, and the products were identified by GC-MS. The reaction mixture was diluted with ether and treated with 0.5 N HCl (15 mL). The organic layer was separated, and the aqueous layer was extracted with ether (4 × 25 mL). The combined organic layers were washed with 10% $NaHCO_3$ solution (2 × 15 mL), with 10% $Na_2S_2O_3$ solution (1 × 10 mL) and brine and dried over anhydrous Na_2SO_4. Solvent was removed by rotary evaporation and the crude product was purified by silica gel chromatography using hexane as eluent to give the corresponding alkenyl iodide **10a–l**.

1-(1-Iodoethenyl)benzene (10a)[50]. Colorless oil (yield 90%): IR (neat) ν 3057, 1559, 1487, 896, 767, 697 cm^{-1}; ^{1}H NMR (400 MHz) δ = 7.34-7.28 (m, 3H, Arom.), 7.53-7.48 (m, 2H, Arom.), 6.47 (d, 1H, J = 1.7 Hz), 6.10 (d, 1H, J = 1.7 Hz); ^{13}C NMR (100 MHz) δ = 140.3, 127.0, 126.5, 125.9, 120.9, 102.3; EI-MS m/z = 230 [M$^+$], 127, 103 (100) [M$^+$ – I], 77, 51, 39.

1-(1-Iodoethenyl)-2-methylbenzene (10b). Colorless oil (yield 95%): IR (neat) ν 3062, 1618, 1455, 905, 763, 627 cm^{-1}; ^{1}H NMR (200 MHz) δ = 7.30-7.23 (m, 4H, Arom.), 6.23 (d, 1H, J = 1.4 Hz), 6.18 (d, 1H, J = 1.4 Hz), 2.44 (s, 3H); ^{13}C NMR (50 MHz) δ = 140.9, 132.9, 128.1, 127.2, 125.9, 124.8, 122.6, 104.2, 21.3; EI-MS m/z = 244 [M$^+$], 127, 117 (100) [M$^+$ – I], 115, 91, 65, 51, 39. Anal. C_9H_9I requires: C, 44.29; H, 3.72%; found: C, 44.25; H, 3.58%.

1-(1-Iodoethenyl)-2-methoxybenzene (10c)[51]. Colorless oil (yield 95%): IR (neat) ν 3038, 1600, 1459, 1251, 1041, 902, 750 cm^{-1}; ^{1}H NMR (400 MHz) δ = 7.33-7.25 (m, 2H, Arom.), 6.95-6.87 (m, 2H, Arom.), 6.30 (d, 1H, J = 1.0 Hz), 6.18 (d, 1H, J = 1.0 Hz), 3.90 (s, 3H); ^{13}C NMR (100 MHz) δ = 190.1, 128.3, 125.9, 122.5, 121.0, 120.5, 112.3, 104.8, 61.5; EI-MS m/z = 260 [M$^+$], 133 (100) [M$^+$ – I], 127, 118, 105, 89, 77, 51, 39. Anal. C_9H_9IO requires: C, 41.56; H, 3.49%; found: C, 41.53; H, 3.44%.

1-(1-Iodoethenyl)-4-bromobenzene (10d)[52]. Pale yellow oil (yield 80%): IR (neat) ν 3086, 1583, 1485, 1077, 892, 793 cm^{-1}; ^{1}H NMR (200 MHz) δ = 7.48-7.27 (m, 5H, Arom.), 6.47 (d, 1H, J = 1.9 Hz), 6.10 (d, 1H, J = 1.9 Hz); ^{13}C NMR (50 MHz) δ = 140.2, 129.9, 129.1, 127.6, 122.5, 105.2; EI-MS m/z = 310 and

308 [M+], 183 and 185 (100) [M+ – I], 127, 102, 75, 63, 51. Anal. C_8H_6BrI requires: C, 31.10; H, 1.96%; found: C, 31.07; H, 1.93%.

1-(1-Iodoethenyl)-4-(trifluoromethyl)benzene (10e)[52]. Pale yellow oil (yield 75%): IR (neat) ν 3077, 1594, 1409, 1055, 849, 790 cm^{-1}; ^1H NMR (400 MHz) $\delta = 7.60$ (d, 2H, $J = 1.1$ Hz, Arom.), 6.42 (d, 1H, $J = 1.9$ Hz), 6.07 (d, 1H, $J = 1.9$ Hz); ^{13}C NMR (100 MHz) $\delta = 159.7, 135.2, 130.3, 128.6, 128.0, 127.6, 126.8, 121.7, 120.3, 117.3, 114.0, 11.7, 104.6, 60.1$; EI-MS $m/z =$ 286 [M+], 159 (100) [M+ – I], 140, 127, 75, 65, 51, 39. Anal. $C_9H_6F_3I$ requires: C, 34.85; H, 5.85%; found: C, 32.20; H, 6.12%.

1-(3-Iodo-3-butenyl)benzene (10f)[53]. Pale red oil (yield 90%): IR (neat) ν 3039, 3016, 1595, 1422, 1027, 985, 722 cm^{-1}; ^1H NMR (400 MHz) $\delta = 7.37$-7.31 (m, 2H, Arom.), 7.28-7.19 (m, 3H, Arom.), 5.97 (d, 1H, $J = 1.9$ Hz), 5.70 (d, 1H, $J = 1.9$ Hz), 2.85 (t, 2H, $J = 6.9$ Hz), 2.68 (t, 2H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz) $\delta = 135.3, 128.6, 126.9, 126.0, 119.7, 105.1, 45.7, 39.3$; EI-MS $m/z = 258$ [M+], 131 (100) [M+ – I], 127, 91, 77, 65, 51, 39. Anal. $C_{10}H_{11}I$ requires: C, 46.54; H, 4.30%; found: C, 46.57; H, 4.29%.

(*Z*)- and (*E*)-1-(1-Iodo-1-propenyl)benzene (10g)[54]. Pink liquid (yield 90%), which was determined by ^1H NMR analysis to be an 95 : 05 mixture of iodides (*Z*)- and (*E*)-**10g**: IR (neat) ν 3056, 1681, 1487, 1441, 851, 753, 693, 627 cm^{-1}; EI-MS $m/z = 244$ [M+], 127, 117 (100) [M+ – I], 102, 91, 76, 63, 51, 39. Anal. C_9H_9I requires: C, 44.29; H, 3.72%; found: C, 44.25; H, 3.70%. The major isomer in acetonitrile was identified as iodide (*Z*)-**10g**: ^1H NMR (200 MHz) $\delta = 7.58$-7.53 (m, 2H, Arom.), 7.45-7.33 (m, 3H, Arom.), 6.06 (q, 1H, $J = 6.6$ Hz), 2.05 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (50 MHz) $\delta =$ 137.9, 131.4 128.3, 126.2, 125.8, 105.2, 20.2. The major isomer in toluene was identified as iodide (*E*)-**10g**: ^1H NMR (200 MHz) $\delta =$ 7.44-7.31 (m, 5H, Arom.), 6.67 (q, 1H, $J = 7.2$ Hz), 1.72 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (50 MHz) $\delta = 139.0, 129.7, 128.2, 126.5, 126.2, 103.1, 15.8$.

(*Z*)- and (*E*)-1-(1-Iodo-3-methyl-1-butenyl)benzene (10h)[55]. Colorless oil (yield 82%), which was determined by ^1H NMR analysis to be an 92 : 08 mixture of iodides (*Z*)- and (*E*)-**10h**: IR (neat) ν 3056, 1625, 1442, 755, 616 cm^{-1}; EI-MS $m/z = 272$ [M+], 145 (100) [M+ – I], 129, 127, 117, 91, 77, 51, 39. Anal. $C_{11}H_{13}I$ requires: C, 48.55; H, 4.82%; found: C, 48.51; H, 4.79%. The major isomer in acetonitrile was identified as iodide (*Z*)-**10h**: ^1H NMR (200 MHz) $\delta = 7.51$-7.29 (m, 5H, Arom.), 5.72 (d, 1H, $J =$ 8.4 Hz), 2.80-2.70 (m, 1H), 1.15 (d, 6H, $J = 6.6$ Hz); ^{13}C NMR (50 MHz) $\delta = 142.7, 139.1, 128.6, 127.3, 125.9, 100.1, 29.5, 20.3$. The major isomer in toluene was identified as iodide (*E*)-**10h**: ^1H NMR (200 MHz) $\delta = 7.51$-7.29 (m, 5H, Arom.), 6.35 (d, 1H, $J =$ 10.2 Hz), 2.38-2.30 (m, 1H), 1.00 (d, 6H, $J = 6.6$ Hz); ^{13}C NMR (50 MHz) $\delta = 148.3, 143.0, 128.4, 126.9, 125.7, 99.0, 23.7, 20.5$.

Methyl (*Z*)-3-iodo-2-propenoate (10i)[56]. Pale yellow oil (yield 93%): IR (neat) ν 3025, 1728, 1597, 1205, 1166 cm^{-1}; ^1H NMR (200 MHz) $\delta = 7.39$ (d, 1H, $J = 8.8$ Hz), 6.81 (d, 1H, $J = 8.8$ Hz), 3.66 (s, 3H); ^{13}C NMR (50 MHz) $\delta = 164.2, 129.5, 95.0, 52.3$; EI-MS $m/z = 212$ (100) [M+], 181, 153, 127, 85, 59, 53, 29.

(*Z*)- and (*E*)-4-Iodo-phenyl-3-buten-2-one (10j)[57]. Pink liquid (yield 84%), which was determined by ^1H NMR analysis to be an 96 : 04 mixture of iodides (*Z*)- and (*E*)-**10j**: IR (neat) ν 3056, 1694, 1567, 1488, 1170, 975, 757, 693 cm^{-1}; EI-MS $m/z = 272$ [M+], 145 [M+ – I], 129, 127, 102, 76, 51, 43 (100). Anal. $C_{10}H_9IO$ requires: C, 44.14; H, 3.33%; found: C, 44.10; H, 3.28%. The major isomer in acetonitrile was identified as iodide (*Z*)-**10j**: ^1H NMR (400 MHz) $\delta = 7.53$-7.50 (m, 2H, Arom.), 7.37-7.35 (m, 3H, Arom.), 6.99 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz) $\delta = 200.8, 143.0, 135.8, 128.7, 127.4, 126.4, 105.1, 44.3$. The major isomer in toluene was identified as iodide (*E*)-**10j**: ^1H NMR (400 MHz) $\delta = 7.68$-7.65 (m, 2H, Arom.), 7.44-7.42 (m, 3H, Arom.), 7.04 (s, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz) $\delta = 200.2, 137.2, 133.5, 128.6, 128.0, 126.9, 101.5, 44.5$.

(*Z*)-3-Iodo- and (*Z*)-2-iodo-2-butenylbenzoate (10l and 11l)[58]. Colorless oil (yield 79%), which was determined by ^1H NMR analysis to be an 92 : 08 mixture of 3-iodo-**2l** and 2-iodo-**2l**: IR (neat) ν 3049, 1731, 1596, 1214, 1129, 772, 618 cm^{-1}; EI-MS $m/z =$ 175 [M+ – I], 127, 105 (100), 77, 51, 39. The major isomer was identified as (*Z*)-3-iodo-**10l**: ^1H NMR (400 MHz) $\delta = 8.06$-8.04 (m, 2H, Arom.), 7.58-7.46 (m, 1H, Arom.), 7.45-7.42 (m, 2H, Arom.), 5.90-5.87 (m, 1H), 4.85 (d, 1H, $J = 1.3$ Hz), 4.83 (d, 1H, $J = 1.3$ Hz), 2.58 (d, 3H, $J = 1.3$ Hz); ^{13}C NMR (100 MHz) $\delta = 166.5, 133.4, 133.2, 129.9, 129.7, 128.5, 104.7, 69.3, 34.0$. The minor isomer was identified as (*Z*)-2-iodo-**11l**: ^1H NMR (400 MHz) $\delta = 8.06$-8.04 (m, 2H, Arom.), 7.58-7.46 (m, 1H, Arom.), 7.45-7.42 (m, 2H, Arom.), 6.13-6.08 (m, 1H), 5.01 (d, 2H, $J = 1.3$ Hz), 1.83 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz) $\delta = 166.3, 135.2, 130.1, 128.6, 128.5, 102.1, 72.4, 21.8$.

Convergent synthesis of (*R*)-Tiagabine

2-Iodo-3-methylthiophene (8)

To a solution of commercially available of 3-methylthiophene (3 g, 30.61 mmol) in benzene (10 mL) were added in small portions mercuric oxide (6.12 g, 28.30 mmol) and iodine (7.95 g, 31.4 mmol) at 0 °C. The mixture was stirred at room temperature for 0.5 h, and the precipitate was filtered and washed with ether. The filtrate and washings were washed with aqueous $Na_2S_2O_3$ and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography of silica gel and hexane as eluent to provide 5 g (yield 73%) of the title product **8** as a pale-red liquid: IR (neat) ν 3029, 1374, 1211, 1093, 961, 825, 737 cm^{-1}; ^1H NMR (400 MHz) $\delta = 7.35$ (d, 1H, $J = 5.6$ Hz), 6.76 (d, 1H, $J = 5.5$ Hz), 2.23 (s, 3H); ^{13}C NMR (50 MHz) $\delta =$ 142.8, 130.3, 129.1, 74.6, 18.2; EI-MS $m/z = 224$ [M+], 127, 97 (100) [M+ – I], 69, 53, 45. Anal. C_5H_5IS requires: C, 26.80; H, 2.25; S, 14.31%; found: C, 26.77; H, 2.19; S, 14.29%.

4-(3-Methyl-2-thienyl)-3-butyn-1-ol (12). A mixture of 2-iodo-3-methylthiophene (**8**) (1.5 g, 6.69 mmol), 10% Pd/C (0.174 mmol), PPh_3 (0.35 g, 1.34 mmol), CuI (0.064 g, 0.335 mmol) and ethanolamine (1.22 g, 20.07 mmol) in water (40 mL) was stirred at 25 °C for 30 min under nitrogen. The 3-butyn-1-ol (0.70 g, 10.03 mmol) was added, and the mixture was initially stirred at room temperature for 1 h and then at 80 °C for 18 h. After completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and filtered through Celite. The organic layer was separated and the aqueous layer was extracted with additional ethyl acetate (5 × 25 mL), and the combined organic phases were washed with water (2 × 15 mL) and brine (2 × 15 mL), and dried over anhydrous Na_2SO_4. The

solvent was removed and the crude residue was purified by column chromatography on silica gel, using hexane–ethyl acetate (70 : 30) to afford the desired 4-(3-methyl-2-thienyl)-3-butyn-1-ol (**12**) as white solid (1.0 g, yield 90%): m.p. 50–53 °C; IR (nujol) ν 3350, 1422, 1043, 831, 712 cm^{-1}; ^{1}H NMR (400 MHz) $\delta = 7.06$ (d, 1H, $J = 5.1$ Hz), 6.78 (d, 1H, $J = 5.1$ Hz), 3.80 (t, 2H, $J = 6.4$ Hz), 2.72 (d, 2H, $J = 6.0$ Hz), 2.27 (s, 3H); ^{13}C NMR (100 MHz) $\delta = 142.1$, 129.1, 125.1, 118.7, 92.7, 75.3, 61.1, 24.3, 15.0; EI-MS $m/z = 166$ [M$^+$], 135 (100), 91, 77, 65, 51, 39. Anal. $C_9H_{10}OS$ requires: C, 65.02; H, 6.06; S, 19.29%; found: C, 64.97; H, 6.03; S, 19.29%.

2-(4-Bromo-1-butynyl)-3-methylthiophene (13). To a solution of **12** (0.65 g, 3.91 mmol) in dry CH_2Cl_2 (15 mL) was added CBr_4 (1.55 g, 4.69 mmol) at –30 °C in one portion. The mixture was stirred vigorously for 10 min, and a solution of PPh_3 (1.24 g, 4.57 mmol) in dry CH_2Cl_2 (10 mL) was added. The solution was stirred for 2 h at –30 °C, warmed up to 0 °C, and then stirred another hour. The crude reaction mixture was filtered through a thin layer of silica gel, concentrated *in vacuo*, and after purification by column chromatography on silica gel, using hexane–ethyl acetate (90 : 10) as eluent, 0.79 g of 2-(4-bromo-1-butynyl)-3-methylthiophene (**13**) was obtained (yield 88%): IR (neat) ν 3027, 1400, 1210, 954, 713 cm^{-1}; ^{1}H NMR (200 MHz) $\delta = 7.10$ (d, 1H, $J = 5.1$ Hz), 6.81 (d, 1H, $J = 5.1$ Hz), 3.53 (t, 2H, $J = 7.3$ Hz), 3.03 (d, 2H, $J = 7.3$ Hz), 2.31 (s, 3H); ^{13}C NMR (50 MHz) $\delta = 142.6$, 129.3, 125.4, 118.5, 92.8, 75.6, 29.7, 24.4, 15.1; EI-MS $m/z = 230$ [M$^+$ + 2], 228 [M$^+$], 147, 135 (100), 115, 91, 77, 63. Anal. C_9H_9BrS requires: C, 47.18; H, 3.96; S, 13.99%; found: C, 47.14; H, 3.92; S, 13.95%.

Ethyl (3*R*)-1-[4-(3-methyl-2-thienyl)-3-butynyl]hexahydro-3-pyridinecarboxylate (4). The heteroaryl substituted compound **13** (0.40 g, 1.74 mmol) was dissolved in acetone (10 mL) and to it were added ethyl (*R*)-3-piperidinecarboxylate tartrate salt (0.54 g, 1.74 mmol), potassium iodide (0.028 g, 0.174 mmol) and potassium carbonate (0.48 g, 3.48 mmol). The mixture was kept stirring for 3 days. The reaction mixture was then filtered and the solvent was evaporated to give an oil residue which was purified by column chromatography on silica gel (hexane–ethyl acetate 50 : 50) to give **4** (0.41 g, yield 78%) as a yellow oil: IR (neat) ν 3032, 1731, 1446, 1179, 1032, 711 cm^{-1}; ^{1}H NMR (400 MHz) $\delta =$ 7.04 (d, 1H, $J = 5.1$ Hz), 6.78 (d, 1H, $J = 5.1$ Hz), 4.12 (q, 2H, $J = 4.3$ Hz), 3.03 (dd, 1H, J = 11.1 and 2.9 Hz), 2.81 (d, 1H, $J =$ 11.1 Hz), 2.72-2.61 (m, 4H), 2.58-2.52 (m, 1H), 2.29 (t, 1H, $J =$ 8.5 Hz), 2.27 (s, 3H), 2.12 (dt, 1H, $J = 10.7$ and 2.9 Hz), 1.94 (dd, 1H, $J = 12.8$ and 3.8 Hz), 1.73 (dt, 1H, $J = 13.3$ and 3.8 Hz), 1.45 (qt, 1H, $J = 15.5$ and 3.8 Hz), 1.41 (dd, 1H, $J = 11.5$ and 2.6 Hz), 1.24 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz) $\delta = 174.4$, 141.8, 125.2, 124.8, 123.2, 94.7, 74.3, 60.6, 57.7, 55.3, 53.2, 42.1, 27.1, 24.8, 18.3, 15.0, 14.5; EI-MS $m/z = 305$ [M$^+$], 170 (100), 142, 95. Anal. $C_{17}H_{23}NO_2S$ requires: C, 66.85; H, 7.59; N, 4.59; S, 10.50%; found: C, 66.86; H, 7.63; N, 4.57; S, 10.27%.

Ethyl (3*R*)-1-[(*Z*)- and (*E*)-4-iodo-4-(3-methyl-2-thienyl)-3-butenyl]hexahydro-3-pyridinecarboxylate (14). To a stirred suspension of ethyl (3*R*)-1-[4-(3-methyl-2-thienyl-3-butynyl]-hexahydro-3-pyridinecarboxylate (**4**) (0.23 g, 0.75 mmol) and NaI (0.34 g, 2.26 mmol) in acetonitrile (15 mL) was added $CeCl_3 \cdot 7H_2O$ (0.42 g, 1.12 mmol), and the resulting mixture was stirred at reflux for 24 h. The hydroiodination adduct was extracted from the solid mass by filtration chromatography over a short plug of neutral alumina using diethyl ether as solvent. The filtrate was washed with aqueous 10% $NaHCO_3$ solution, with aqueous 10% $Na_2S_2O_3$, and with saturated NaCl solution, and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the crude residue was further purified by column chromatography over silica gel (90 : 10 hexane–THF) to give 0.3 g (yield 94%) of the 99 : 01 mixture (***Z*)-14** and (***E*)-14** as a pale red liquid: IR (neat) ν 3028, 3021, 1731, 1600, 1200, 781, 624 cm^{-1}; ^{1}H NMR (400 MHz) $\delta =$ 6.75-6.71 (m, 2H), 6.54 (t, 0.1 × 1H, $J = 10.4$ Hz, (*E*)-isomer), 5.74 (t, 0.9 × 1H, $J = 6.4$ Hz, (*Z*)-isomer), 4.11-4.05 (m, 2H), 2.98-2.14 (m, 8H), 2.12 (s, 0.9 × 3H), 2.02 (s, 0.9 × 3H), 2.00-1.39 (m, 5H), 1.21 (t, 0.9 × 3H, $J = 6.8$ Hz), 1.20 (t, 0.1 × 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, *Z*/*E* mixture) $\delta = 174.4$, 146.4, 141.1, 141.0, 135.6, 134.8, 130.7, 130.4, 129.9, 124.9, 124.4, 123.9, 93.6, 85.6, 60.5, 57.3, 56.8, 55.6, 55.4, 53.7, 42.1, 42.0, 35.3, 30.3, 27.1, 24.8, 24.7, 15.2, 14.8, 14.4; EI-MS $m/z = 306$, 296, 170 (100), 142, 127, 99, 42. Anal. $C_{17}H_{24}INO_2S$ requires: C, 47.12; H, 5.58; N, 3.23; S, 7.40%; found: C, 47.09; H, 5.53; N, 3.20; S, 7.37%.

Ethyl (3*R*)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]hexahydro-3-pyridinecarboxylate (15). A 25 mL two-neck round bottom flask containing a magnetic stir bar was charged with alkenyl iodide **14** (0.15 g, 0.35 mmol), under a nitrogen atmosphere. To the flask was added a solution of tetrakis(triphenylphopshine)palladium(0) (9 mg, 0.008 mmol) in dimethoxyethane (1.5 mL) and aqueous Na_2CO_3 solution (2M, 0.35 mL, 0.7 mmol). The resultant solution was stirred at room temperature for 15 min, then a solution of 3-methyl-2-thienylboronic acid (62 mg, 0.437 mmol) in ethanol (1.5 mL) was added dropwise by syringe. The reaction mixture was heated to 90 °C and stirred for 2 h. The solution was cooled to room temperature and filtered through a pad of Celite using dichloromethane, and dried over $MgSO_4$. The solvent was evaporated and the crude chromatographed on silica gel column (EtOAc–hexane 20 : 80) to afford the title compound **15** (0.1 g, yield 76%) as a colorless oil: IR (neat) ν 3037, 3021, 1731, 1614, 1179, 711, 631 cm^{-1}; ^{1}H NMR (400 MHz) $\delta = 7.30$ (d, 1H, $J = 5.1$ Hz), 7.04 (d, 1H, $J = 5.1$ Hz), 6.83 (d, 1H, $J = 5.1$ Hz), 6.76 (d, 1H, $J = 5.1$ Hz), 6.04 (t, 1H, $J =$ 7.7 Hz), 4.11 (q, 2H, $J = 7.3$ Hz), 2.97 (d, 1H, $J = 9.4$ Hz), 2.74 (d, 1H, $J = 11.1$ Hz), 2.57-2.47 (m, 3H), 2.36-2.31 (m, 2H), 2.14 (t, 1H, $J = 10.3$ Hz), 2.04 (s, 3H), 2.02 (s, 3H), 1.94 (qd, 2H, $J =$ 10.7 and 2.6 Hz), 1.69 (dt, 1H, $J = 13.2$ and 3.4 Hz), 1.56 (qt, 1H, $J = 11.5$ and 3.4 Hz), 1.42 (qd, 1H, $J = 11.5$ and 3.8 Hz), 1.24 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz) $\delta = 174.3$, 139.8, 135.5, 135.4, 133.7, 133.5, 131.3, 129.7, 128.3, 124.4, 122.8, 58.3, 55.4, 53.6, 42.0, 27.6, 27.1, 24.7, 15.0, 14.5, 14.3; EI-MS $m/z = 403$ [M$^+$], 358, 170 (100), 142, 111, 99. Anal. $C_{22}H_{29}NO_2S_2$ requires: C, 65.47; H, 7.24; N, 3.47; S, 15.89%; found: C, 65.46; H, 7.20; N, 3.60; S, 15.87%.

(3*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]hexahydro-3-piperidinecarboxylic acid hydrochloride (16). To a solution of Tiagabine ethyl ester **14** (75 mg, 0.18 mmol) in EtOH abs. (5 mL) was added at room temperature 12 M aqueous NaOH (0.5 mL). The reaction mixture was stirred for 4 h at room temperature and then cooled to 5 °C. The pH was adjusted to *ca.* 1 with 4 N aqueous HCl, CH_2Cl_2 (30 mL) was added, and the phases were separated. The organic phase was washed with water (5 mL), with saturated NaCl solution (5 mL), and dried over Na_2SO_4. The solvent was

removed *in vacuo* and the crude product was crystallized from 2-propanol (15 mL) to provide **16** (55 mg, yield 81%) as a white solid: m.p. 184–185 °C; $[\alpha]_D^{25} = -9.98$ ($c = 1.0$, H_2O); ^1H NMR (400 MHz) $\delta = 9.85$ (bs, 1H), 7.22 (d, 1H, $J = 5.1$ Hz), 7.05 (d, 1H, $J = 5.1$ Hz), 6.85 (d, 1H, $J = 5.1$ Hz), 6.74 (d, 1H, $J = 5.1$ Hz), 5.95 (t, 1H, $J = 6.8$ Hz), 3.45-2.40 (m, 9H), 2.00 (s, 3H), 1.95 (s, 3H), 1.87-1.22 (m, 4H); ^{13}C NMR (100 MHz, D_2O) $\delta = 175.3$, 136.7, 134.1, 131.8, 128.5, 130.3, 128.9, 128.5, 125.6, 124.3, 56.3, 53.5, 52.6, 39.7, 24.8, 24.4, 23.4, 22.2, 14.1, 13.7; ESI-MS $m/z =$ 398 [M – HCl + Na], 376 [M – HCl + H]. Anal. $C_{20}H_{26}ClNO_2S_2$ requires: C, 58.30; H, 6.36; N, 3.40; S, 15.57%; found: C, 58.28; H, 6.32; N, 3.43; S, 15.59%.

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