JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

# Asymmetric Synthesis and Biological Evaluation of Natural or Bioinspired Cytotoxic $C_2$-Symmetrical Lipids with Two Terminal Chiral Alkynylcarbinol Pharmacophores

Dymytrii Listunov,[†,‡,§,∥] Isabelle Fabing,[∥] Nathalie Saffon-Merceron,[⊥] Hafida Gaspard,[∥] Yulian Volovenko,[§] Valérie Maraval,*[,†,‡] Remi Chauvin,*[,†,‡] and Yves Génisson*[,∥]

[†]UPR CNRS 8241, LCC, Université de Toulouse, 205 route de Narbonne, F-31077 Toulouse, France

[‡]Université de Toulouse, Université Paul Sabatier, INPT, F-31077 Toulouse, France

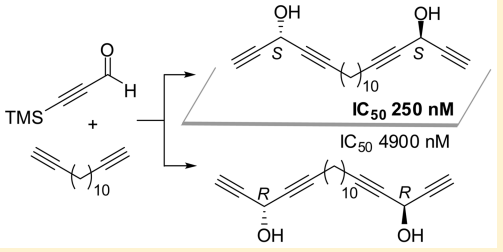
[§]Kiev National Taras Shevchenko University, 60 Volodymyrska Street, 01033 Kiev, Ukraine

[∥]UMR CNRS 5068, LSPCMIB, Université Paul Sabatier, 118 route de Narbonne, Toulouse, 31062 Cedex 9, France

[⊥]Institut de Chimie de Toulouse, ICT FR 2599, Université Paul Sabatier - Toulouse III, Toulouse 31062 Cedex 9, France

Supporting Information

**ABSTRACT:** Bidirectional syntheses of $C_2$-symmetrical lipids embedding two terminal alkynylcarbinol pharmacophores are reported. Naturally occurring chiral alkenylalkynylcarbinol units were generated using Pu's procedure for enantioselective addition of terminal alkynes to aldehydes, allowing the first asymmetric synthesis of (3*R*,4*E*,16*E*,18*R*)-icosa-4,16-diene-1,19-diyne-3,18-diol, isolated from *Callyspongia pseudoreticulata*. Two synthetic analogues embedding the recently uncovered (*S*)-dialkynylcarbinol pharmacophore were secured using Carreira's procedure adapted to ynal substrates. The dramatic effect of the carbinol configuration on cytotoxicity was confirmed with submicromolar $IC_{50}$ values against HCT116 cells.




## INTRODUCTION

Certain acetylenic lipids constitute a family of natural compounds that appear in marine sponges and combine unusual structural features with a wide array of biological activities.[1] Apart from an exceptionally long unbranched aliphatic skeleton, counting up to more than 40 carbon atoms, the main characteristic of these functional lipids is the recurrence of various chiral alkynylcarbinol units.[2] Within this family, a series of $C_2$-symmetrical representatives constitutes a remarkable class of inter-related compounds such as petrosynol (**1**) and congeners (Figure 1).[3] The two terminal alkenylalkynylcarbinol motifs of petrosynols are also found in the C30 backbone of other natural derivatives exhibiting either cyclized, dehydroxylated, or reduced central cores, such as adociacetylenes[4] (see adociacetylene B (**2**), Figure 1), dideoxypetrosynols[5] (see dideoxypetrosynol A (**3**), Figure 1), or duryne[6] (**4**), respectively (Figure 1). Such $C_2$-symmetrical derivatives notably display significant antitumor activities, with $IC_{50}$ values in the submicromolar range for dideoxypetrosynols,[5] durynes,[6] or the C46 parent fulvinol.[7] In addition, the pro-apoptotic activity of many of these natural products was demonstrated.[8] Their intriguing chemical structures have prompted efforts in synthetic chemistry during the past decade,[2,9] but investigations of the structure−activity relationships have only recently emerged. While the presence of the terminal alkenylalkynylcarbinol ((3*S*,4*E*)-en-1-yn-3-ol) fragment was shown to be essential to their cytotoxicity and pro-apoptotic behavior,[10] the influence of the central core has not been described.[2] To delineate further pharmacological opportunities, however,

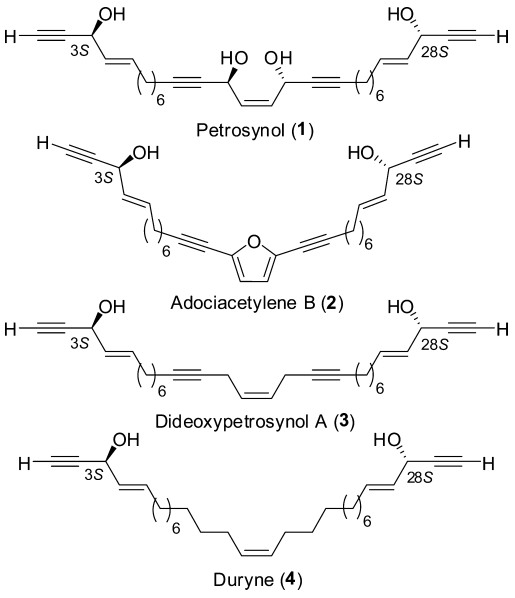



**Figure 1.** Representative $C_2$-symmetrical marine acetylenic lipids.

**Received:** March 18, 2015
**Published:** May 11, 2015





DOI: 10.1021/acs.joc.5b00494
*J. Org. Chem.* 2015, 80, 5386−5394

straightforward enantioselective routes to simplified structures need to be developed.

The first chemistry-driven systematic structure−activity study of the chiral functional alkynylcarbinol fragment as a cytotoxic pharmacophore was recently reported.[11] This revealed the remarkable influence of the absolute configuration of the carbinol center on the antitumor activity, with the (*R*)-like stereochemistry (in reference to the enantiomer of the natural (3*S*,4*E*)-en-1-yn-3-ol pharmacophore shown in Figures 1 and 2) leading to the strongest potency. Additionally, novel

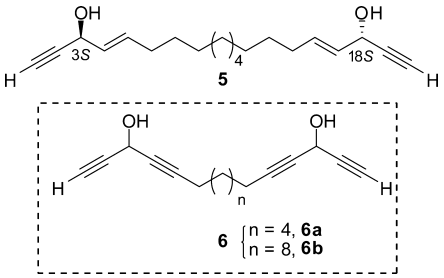



**Figure 2.** Marine compound **5** and related generic target structure **6**.

pharmacophore variants were envisaged, and the (3*S*)-1,4-diyn-3-ol dialkynylcarbinol fragment was identified as both the most active and the most synthetically accessible. These findings originated from the implementation of reliable methods for the preparation of enantioenriched alkynylcarbinol fragments through enantiocontrolled addition of terminal alkynes (so-called "asymmetric alkynylation") onto enals or ynals. The extension of this methodology to the preparation of $C_2$-symmetrical derivatives and the evaluation of their antitumor activity are reported thereafter.

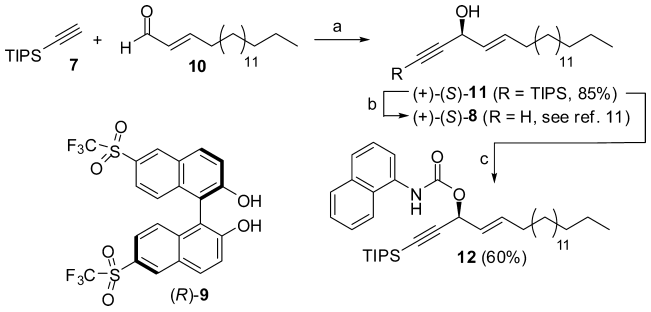
## RESULTS AND DISCUSSION

The simple $C_2$-symmetrical C20 product **5**, isolated from *Callyspongia pseudoreticulata*, was selected as a basis for the study of related generic bis-dehydro representatives of type **6** (Figure 2).[12] Originally isolated as the (3*S*,18*S*) stereoisomer,[12a] both enantiomers of **5** were also recently extracted from *Callyspongia* sp.[12b] These enantiomers were prepared through enzymatic kinetic resolution, and a series of related compounds, including racemic analogues with different chain lengths, were also reported for comparative cell viability studies.

The natural product **5** itself was first targeted. Taking advantage of the ideal $C_2$-symmetry of the molecule, a double-elongation approach was envisaged to rapidly assemble the functionalized C20 backbone in a stereocontrolled fashion. Efficient methods to prepare alkenylalkynylcarbinol fragments by asymmetric alkynylation of enals have appeared only recently.[13] Trost developed a prophenol/$Me_2Zn$-based procedure[14] that was applied to a bidirectional enantioselective synthesis of adociacetylene B.[15] The Ti(O-*i*-Pr)$_4$/BINOL-catalyzed procedure reported by Pu for the asymmetric alkynylation of aldehydes by in situ generated Zn-acetylide[16] was here selected for the elaboration of the key 4(*E*)-en-1-yn-3-ol moieties using TIPS-acetylene (**7**) as nucleophile.

Before exploring Pu's method with a bis-electrophile en route to **5**, the reaction was first probed in the preparation of the naturally occurring lipidic monocarbinol 3(*S*)-eicos-4(*E*)-en-1-yn-3-ol (**8**) (Scheme 1).[17] In view of generating a more Lewis acidic Ti complex, the use of an activated BINOL ligand **9**[18] bearing two highly electron-withdrawing triflone substituents in

**Scheme 1. Synthesis of the Natural Product 3(*S*)-Eicos-4(*E*)-en-1-yn-3-ol (8)**[a]




[a]Reagents and conditions: (a) (i) $Et_2Zn$, PhMe, reflux, (ii) (*R*)-**9**, Ti(O-*i*-Pr)$_4$, $Et_2O$, rt; (b) see ref 11; (c) 1-naphthyl isocyanate, DMAP, $K_2CO_3$, $CH_2Cl_2$, rt.

the 6,6′-positions was examined.[19] Performing the asymmetric alkynylation reaction of (*E*)-octadec-2-enal (**10**) with ligand (*R*)-**9** led to the expected carbinol (+)-**11** in 85% yield, to be compared with the 75% yield obtained using standard BINOL. In view of determining the ee by chiral supercritical fluid chromatography (SFC), the enantioenriched carbinol (+)-**11** was first converted into the corresponding naphthyl carbamate **12** so as to maximize both UV detection and diastereodifferentiation on the chiral stationary phase.[11] Analytical chiral SFC indicated an ee value of 81% for **12**, comparable to what was previously obtained with (*R*)-BINOL. The activated BINOL **9** giving rise to a more efficient transformation leads to prospects for further optimization of the Pu's method.

A crystalline sample of the carbamate **12** proved suitable for X-ray diffraction analysis, allowing determination of its absolute configuration (see the Supporting Information, Figure S1).[20] On the basis of a Flack parameter value of −0.08 (16), the crystallographic data unambiguously indicates that an (*S*)-configured alkenylalkynylcarbinol was generated from the reaction with (*R*)-BINOL.

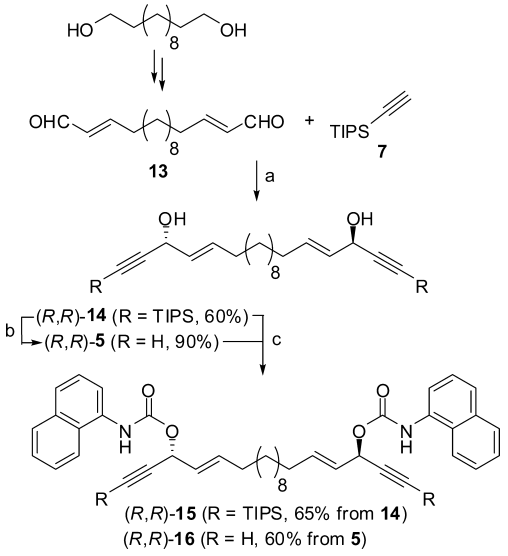
In the $C_2$-symmetrical double-headed series, the bis-enal **13** required for the synthesis of **5** was prepared from commercially available 1,12-dodecandiol through a four-step sequence inspired from the two-step procedure described by Miyamoto.[12b] This method was modified in view of improving the ease of purification of the bis-enal target **13**. Recently, miyakosyne A, a cytotoxic metabolite extracted from the marine sponge *Petrosia* sp. and embedding two alkenylalkynylcarbinol moieties as in **5**, was also reported to be synthesized from a lipidic dienal, the latter being efficiently obtained by a double-olefin cross-metathesis process.[21] The isolation of miyakosyne A was, however, performed by chemoenzymatic resolution of a mixture of isomers. In contrast, the preparation of **5** was envisaged by direct enantioselective synthesis (Scheme 2).

The Zn-acetylide generated upon treatment of TIPS-acetylene (**7**) with $Et_2Zn$ in refluxing toluene was reacted with the bis-electrophile **13** in the presence of the chiral Lewis acidic complex preformed from Ti(O-*i*-Pr)$_4$ and (*S*)-BINOL in $Et_2O$ (Scheme 2). The double adduct of expected structure (*R*,*R*)-**14** was isolated in 60% yield. Treatment with TBAF finally delivered the targeted compound **5**, which was thus obtained in a 54% overall yield from the bis-enal **13**, with analytical data in agreement with those previously reported for (*R*,*R*)-**5**.[12] In order to determine the exact stereochemical composition of the isolated stereoenriched sample of **5**, a



DOI: 10.1021/acs.joc.5b00494
J. Org. Chem. 2015, 80, 5386−5394

**Scheme 2. Synthesis of Enantioenriched Double-Headed $C_2$-Symmetrical Natural Product 5**[a]



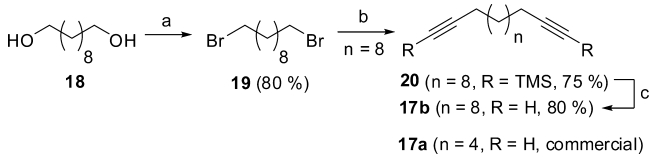

[a]Reagents and conditions: (a) (i) $Et_2Zn$, PhMe, reflux, (ii) **7**, (*S*)-BINOL, $Ti(O\text{-}i\text{-}Pr)_4$, $Et_2O$, rt; (b) TBAF, THF, rt; (c) 1-naphthyl isocyanate, DMAP, $K_2CO_3$, $CH_2Cl_2$, rt.

statistical mixture of all three stereoisomers (*d*/*l*/*meso*) of **14** was also prepared by addition of the lithium TIPS-acetylide onto the bis-enal **13**. The stereoisomeric mixture of alcohols was converted into the corresponding mixture of bis-naphthyl carbamates **15**, which proved inseparable by chiral HPLC or SFC. However, the *d*/*l*/*meso* statistical mixture (0.25:0.25:0.5) of the desilylated bis-carbamate **16** could be resolved by means of SFC (analysis on a Chiralpak IA-3 $\mu$m column eluted with SC $CO_2$/MeOH). A similar SFC analysis of the stereoenriched mixture of **16** obtained by the Pu's method with (*S*)-BINOL as a chiral inducer indicated that the major (*R*,*R*) enantiomer was formed in 94% ee, along with an equimolar amount of the *meso* stereoisomer ((*R*,*R*)/(*S*,*S*)/*meso* = 48.7:1.4:49.9).

For comparison, an ee of ca. 80% was previously observed for the asymmetric addition of TIPS-acetylene **7** onto the C18 monoenal **10** under similar conditions.[11] Although the conditions are not strictly the same (regarding the structure of the enal and the operating stoichiometry), one might assume a comparable asymmetric induction in the course of the first alkynylation of the bis-enal **13** toward the (*R*)-configured monoadduct and deduce that the second alkynylation should thus occur in a much higher diastereoisomeric excess from the minor (*S*)-configured monoadduct ($de_{SR}$ = 70%) than from its enantiomer ($de_{RR}$ = 8%, see the Supporting Information, Scheme S1). A considerable mismatch effect by a factor of ca. 10 ($ee_R/de_{RR}$ = 10) between (*S*)-BINOL and the (*R*)-monoadduct intermediate could therefore be suggested.

Both enantiomers of the dehydro variants **6** of the natural product **5** embedding two dialkynylcarbinol pharmacophore moieties were then targeted. Considering the paucity of reported methodologies for asymmetric alkynylation of ynals, the recently adapted Carreira's protocol[22] for the enantioselective preparation of simple lipidic dialkynylcarbinols[11] was envisaged from bis-terminal diyne substrates. The 1,9-decadiyne (**17a**) was selected as a commercially available precursor of the truncated C16 double-headed target **6a**. The diyne bis-nucleophile **17b** required for the elaboration of the exact bis-dehydro analogue **6b** of the natural C20 bis-alkenyl-alkynylcarbinol **5** was secured in three steps and 48% overall yield from the diol **18** by means of double bromination, addition of lithium TMS-acetylide and desilylation (Scheme 3).

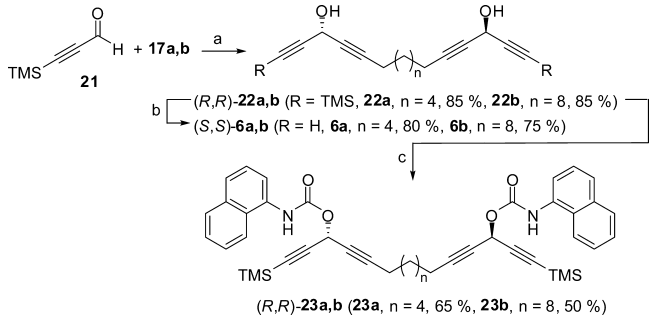
**Scheme 3. Synthesis of the Diyne 17b Envisaged as a Precursor of 6b**[a]




[a]Reagents and conditions: (a) HBr, $H_2O$, 48 h, 100 °C; (b) TMS-acetylene, HMPA, *n*-BuLi, THF, −78 °C to rt; (c) $K_2CO_3$, THF−MeOH (1:1), rt.

Treatment of the diynes **17a**,**b** with $Zn(OTf)_2/Et_3N$ in the presence of (−)-*N*-methylephedrine (NME) as a chiral inducer in $CH_2Cl_2$, followed by addition of the ynal **21**, led to the bis-alkynylated products (*R*,*R*)-**22a**,**b** in 85% yield (Scheme 4).

**Scheme 4. Synthesis of the Dehydro Analogues 6a,b of the Natural Product 5**[a]




[a]Reagents and conditions: (a) (−)-NME, $Zn(OTf)_2$, $Et_3N$, $CH_2Cl_2$, rt; (b) $K_2CO_3$, THF−MeOH (1:1), rt; (c) 1-naphthyl isocyanate, DMAP, $K_2CO_3$, $CH_2Cl_2$, rt.

The diols were then desilylated to afford (*S*,*S*)-**6a**,**b**, the targeted dehydro analogues of **5**. In order to determine the stereoselectivity of the double-Carreira-type procedure, the bis-carbinols (*R*,*R*)-**22a**,**b** were converted into the corresponding 1-naphthyl carbamates (*R*,*R*)-**23a**,**b**. The (*S*,*S*) isomers of **22a**,**b** were also prepared in the same way using (+)-NME as a chiral inducer, thus leading to (*R*,*R*)-**6a**,**b** after desilylation. Conditions for the analytical resolution of a statistical *d*/*l*/*meso* stereoisomeric mixture of **23a**,**b** by chiral SFC (Chiralpak AD-H 5 $\mu$m or IC-3 column, respectively, eluted with a SC $CO_2$/MeOH gradient) were first determined. Chiral analysis of an enantioenriched sample of (*S*,*S*)-**23a** prepared from (*S*,*S*)-**22a** indicated a 78% ee for the *dl* isomers and a *dl*/*meso* ratio of 62:38. Likewise, a 76% ee and a *dl*/*meso* ratio of 77:23 for (*R*,*R*)-**22b** were indicated by chiral SFC analysis of the corresponding stereoenriched bis-carbamate (*R*,*R*)-**23b**. On the basis of previous studies, the (*R*,*R*) absolute configuration was assigned to the major enantiomer formed in the presence of (−)-NME.[21]

A crystalline sample of (*S*,*S*)-**6b** was found suitable for X-ray diffraction analysis, allowing confirmation of the $C_2$-symmetrical structure (Figure 3; for detailed crystallographic data, see the Supporting Information, Table S1).[23]



DOI: 10.1021/acs.joc.5b00494
J. Org. Chem. 2015, 80, 5386−5394

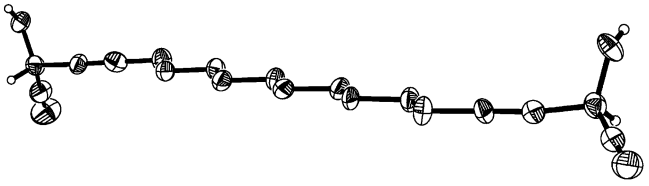


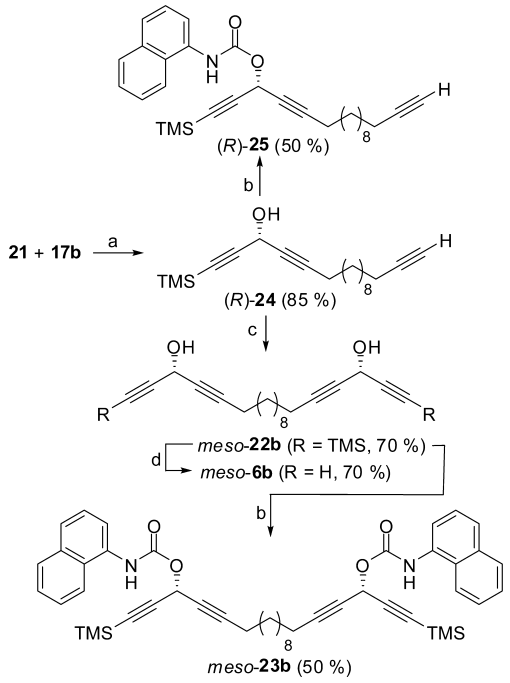
**Figure 3.** Molecular view of the X-ray crystal structure of the bis-dialkynylcarbinol **6b** (Scheme 4), with thermal ellipsoids drawn at the 50% probability level. For clarity, hydrogen atoms (excepted on asymmetric center and oxygen atom) are omitted.[23]

As in the case of **14**, the relatively high proportion of the *meso* stereoisomer of **22a,b** reveals a lowest stereoinduction in the course of the formation of the second carbinol center compared to that of the first alkynylation. The decrease of the *meso*/*dl* ratio vs the increase of the distance between the two terminal reacting centers (*dl*/*meso* 62:38 for **22a** *vs* *dl*/*meso* 84:16 for **22b**) is consistent with such a mismatch effect. For a given chain length ($n$ = 8), the *dl*/*meso* ratio obtained for **22b** (84:16) is, however, higher than that previously observed for the formation of **14** (50:50, Scheme 2), these two products being obtained following two strategies of opposite electro-/nucleophilic polarity (the aldehyde functions are indeed located either at both ends of the lipidic chain of **13** for the synthesis of **14** or on the acetylenic unit of **21** for the synthesis of **22b**). This difference may be due to more facile intramolecular Zn-chelation of the bis-enal **13** used in the preparation of **14**, which would alter the reactivity of its aldehyde electrophilic centers. It is also incidentally correlated with the higher overall freedom degree allowed by the C=C bonds of the dielectrophile **13** as compared with the C≡C bonds of the dinucleophile **17b**.

In view of a selective synthesis of the *meso* stereoisomer of **6b** bearing two heterochiral alkynylcarbinol termini, a two-step sequential route was also explored. Monoaddition of the diyne **17b** onto the ynal **21** was selectively accomplished with 4 equiv of (−)-NME and 1 equiv of electrophile only (Scheme 5). The monoadduct (*R*)-**24**, thus secured in 85% yield, was then converted to the 1-naphthyl carbamate (*R*)-**25** for the determination of the enantiomeric excess by chiral SFC analysis. In agreement with previous studies on the adaptation of the Carreira's procedure for asymmetric alkynylation of ynals, (−)-NME induced the formation of the (*R*) enantiomer in 95% ee. Subsequent addition of (*R*)-**24** onto **21** was run with (+)-NME, affording the bis-adduct *meso*-**22b** in 70% yield. The corresponding bis-carbamate *meso*-**23b** was then prepared, allowing the measurement of a *dl*/*meso* ratio of 11:89 by chiral SFC. From this ratio, a 82% de for the second alkynylation step in favor of the (*S*)-configured dialkynylcarbinol fragment in *meso*-**22b** can be inferred. Deprotection of *meso*-**22b** finally delivered the bis-alkynylcarbinol target *meso*-**6b**.

The naturally occurring acetylenic lipid **5** and the two dehydro analogues **6a,b** were then submitted to cytotoxicity assays. For the sake of comparison with previous studies, the human colon carcinoma HCT116 was selected as a representative cell line.[11] An $IC_{50}$ value of 230 nM at 96 h was measured for the sample of (*R,R*)-**5**. This value is consistent with what has been previously reported for natural or synthetic (*R,R*)-**5** ($IC_{50}$ at 48 h against TR-LE cells of 110 nM and 350 nM).[12b] The unnatural bis-dialkynylcarbinol (*S,S*)-**6b**, dehydro analogue of the C20 natural product (*R,R*)-**5** (the opposite configuration being due to an inversion of the CIP priority between the alkenyl and the alkynyl substituents of the carbinol center) displayed an equivalent cytotoxicity ($IC_{50}$ ≈ 250 nM). It is noteworthy that the single-headed analogue of (*S,S*)-**6b** was described to exhibit a higher cytotoxity with a $IC_{50}$ value of 60−90 nM in the case of the optimized C12 length of the alkyl chain.[11] As reported in the single-headed series, a dramatic influence of the enantiomeric series on cell viability was observed,[11] with (*R,R*)-**6b** being indeed almost 20 times less cytotoxic ($IC_{50}$ ≈ 4900 nM) than its enantiomer. Consistently, the achiral stereoisomer *meso*-**6b** featuring both (*R*)- and (*S*)-alkynylcarbinol termini displayed an intermediate value of $IC_{50}$ (470 nM). The truncated C16 representative (*S,S*)-**6a** ($IC_{50}$ ≈ 1000 nM) was also found to be four times less efficient than (*S,S*)-**6b**, confirming the crucial importance of the spacer length between the two pharmacophoric units.

**Scheme 5. Sequential Synthesis and Derivatization of the *Meso* Isomer of 6b**[a]




[a]Reagents and conditions: (a) (−)-NME, $Zn(OTf)_2$, $Et_3N$, $CH_2Cl_2$, rt; (b) 1-naphthyl isocyanate, DMAP, $K_2CO_3$, $CH_2Cl_2$, rt; (c) **21**, (+)-NME, $Zn(OTf)_2$, $Et_3N$, $CH_2Cl_2$, rt; (d) $K_2CO_3$, THF−MeOH (1:1).

## CONCLUSION

In summary, the Pu and modified Carreira methods for asymmetric alkynylation of enals and ynals were shown to be efficient in the synthesis of $C_2$-symmetrical doubled-headed acetylenic lipids featuring two alkynylcarbinol pharmacophoric units. In the monofunctional version of Pu's method from enals, the formation of an (*S*)-configured alkenylalkynylcarbinol center using (*R*)-BINOL as a chiral inducer was demonstrated by X-ray diffraction analysis. In the difunctional version, double-induction effects were evidenced, and the method allowed the first stereoselective double-elongation approach to the marine compound **5**. Preparation of the hitherto unknown bis-dehydro analogues of **5** was also performed using the previously disclosed modified Carreira's method for ynal substrates. Whereas a one-pot procedure directly afforded the chiral $C_2$-symmetrical *d*/*l* stereoisomers according to a bidirectional strategy, a sequential two-step approach allowed


DOI: 10.1021/acs.joc.5b00494
J. Org. Chem. 2015, 80, 5386−5394

the preparation of the *meso* isomer. Biological evaluations revealed that the double-headed acetylenic lipids (*R*,*R*)-**5** and (*S*,*S*)-**6b** display potent cytotoxicity against HCT116 cells with $IC_{50}$ values in the submicromolar range. For the non-natural bis-dialkynylcarbinol compounds **6b**, a dramatic influence of the configuration of the asymmetric carbinol center was observed, the eutomer corresponding to the (*R*)-like series (in reference to the (3*R*,4*E*)-en-1-yn-3-ol natural alkenyl-alkynylcarbinol pharmacophore). The present results thus open prospects of developments in total synthesis, asymmetric methodology, and multivalent pharmacophore design.

## EXPERIMENTAL SECTION

**General Experimental Details.** The following solvents and reagents were dried and freshly distilled prior to use: $CH_2Cl_2$ (from $CaH_2$), $Et_2O$, THF (from sodium/benzophenone). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F254 precoated plates. Chromatograms were observed under UV light and/or were visualized by heating plates dipped in 10% phosphomolybdic acid in EtOH. Column chromatography was carried out with 35−70 mm flash silica gel. NMR spectroscopic data were obtained with instruments working at 300 or 400 MHz for $^1$H nuclei. Chemical shifts ($\delta$) are reported in ppm relative to the residual solvent peak; *J* values are given in hertz. High-resolution mass spectra (HRMS) were performed by desorption chemical ionization with methane gas (DCI ($CH_4$)) using a TOF mass analyzer. IR analyses were run on an ATR device (4 $cm^{-1}$ of resolution, 16 scans) equipped with a DTGS detector. Optical rotations were measured on a JASCO P-2000 polarimeter; $[\alpha]_D$ values are given in deg $dm^{-1}$ $cm^{-3}$ $g^{-1}$. SFC ($CO_2$) chiral resolutions were run on either a Chiralpak IA-3 (4.6 × 100 mm), Chiralpak IC-3 (4.6 × 100 mm), or Chiralpak AD-H 5 $\mu$m (4.6 × 250 mm) column.

**General Procedures.** *General Procedure A: Preparation of the 1-Naphthyl Carbamates.* 1-Naphthyl isocyanate (1.5 equiv/hydroxyl group), DMAP (0.1 equiv), and alcohol (1 equiv) were taken into an anhydrous $CH_2Cl_2$/pentane (1:1) mixture (1 mL). The reaction mixture was stirred at rt overnight. The solvent was evaporated off, and the crude product was purified by chromatography over $SiO_2$ (pentane/$Et_2O$, 8:2) to give the expected 1-naphthyl carbamate.

*General Procedure B: Preparation of the Stereoisomeric Mixtures of Bis-dialkynyldiols.* *n*-Butyllithium (1.6 M solution in hexanes, 2.2 equiv) was added to a solution of diyne (1 equiv) in anhydrous THF (10 mL) at −78 °C under Ar atmosphere, and the reaction mixture was stirred at this temperature for 30 min. A solution of 3-(trimethylsilyl)propiolaldehyde (**21**) (2.2 equiv) in THF (1 mL) was then added, and the reaction mixture was stirred for 4 h at −78 °C. After addition of an $NH_4Cl$ saturated aqueous solution, the reaction mixture was partitioned between brine and $Et_2O$ and the aqueous phase extracted with $Et_2O$. After standard treatment of the gathered organic layers, the crude product was purified by chromatography over $SiO_2$ (pentane/$Et_2O$, 8:2) to give stereoisomeric mixtures of compounds (70−90% yield) as colorless oils. These stereoisomeric mixtures gave analytical data identical to that of their (*R*,*R*), (*S*,*S*), or *meso* stereoisomers, except for their optical rotation.

*General Procedure C: Enantioselective Synthesis of Bis-dialkynylcarbinols.* A flask was charged with $Zn(OTf)_2$ (8 equiv) and (+)- or (−)-*N*-methylephedrine (8 equiv) and purged with dry argon for 15 min. To the flask were added anhydrous $CH_2Cl_2$ (15 mL) and triethylamine (8 equiv). The resulting mixture was vigorously stirred for 2 h at rt. Then the diyne (1 equiv, in solution in anhydrous $CH_2Cl_2$) was added in one portion. After another 1 h of stirring, the 3-(trimethylsilyl)propiolaldehyde (**21**) (4 equiv) was added, and then the mixture was stirred at rt overnight. A saturated aqueous $NH_4Cl$ solution was added, and the mixture was extracted with $CH_2Cl_2$. After standard treatment of the gathered organic layers, the crude product was submitted to chromatography over $SiO_2$ (pentane/$Et_2O$, 8:2) to give the desired compound.

*General Procedure D: Deprotection of the Silylated Bis-dialkynylcarbinols.* A solution of the silylated precursor (1 equiv) in a THF/MeOH (1:1) mixture (5 mL) containing $K_2CO_3$ (6 equiv) was stirred at rt for 24 h. Then $H_2O$ was added, and the mixture was extracted with $Et_2O$. After standard treatment of the gathered organic layers, the crude product was submitted to chromatography over $SiO_2$ (pentane/$Et_2O$, 8:2) to give the desilylated compound as a white powder.

*(3R,4E,16E,18R)-Icosa-4,16-dien-1,19-diyne-3,18-diol ((R,R)-**5**).* TBAF (270 $\mu$L of a 1 M solution in THF, 4 equiv) was added to **14** (41.2 mg, 0.067 mmol) in solution in THF (0.5 mL) at 0 °C and the resulting mixture was stirred at rt for 2 h. A saturated aqueous $NH_4Cl$ solution was added, and the mixture was extracted with $Et_2O$. After standard treatment of the gathered organic layers, the crude product was submitted to chromatography over $SiO_2$ to give **5** (18 mg, 90%) as a white powder: $R_f$ 0.3 (pentane/$Et_2O$, 3:2); $[\alpha]_D^{20}$ − 26.4 (*c* 2.5, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.01−1.54 (m, 8H), 1.95−2.15 (m, 2H), 2.55 (d, *J* 2.2 Hz, 1H), 4.82 (ddd, *J* 1.1, 2.2, 6.2 Hz, 1H), 5.59 (ddt, *J* 1.5, 6.1, 15.3 Hz, 1H), 5.90 ppm (dtd, *J* 1.2, 6.8, 15.0 Hz, 1H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 28.8, 29.1, 29.4, 29.5, 31.9, 62.7, 74.0, 83.4, 128.4, 134.5 ppm; IR (neat) $\nu$ 3271, 3030, 2919, 2849, 2223, 2111, 2049, 1671, 1466, 1430, 1397, 1263, 1190, 1136, 1085, 1038, 1009, 968, 962, 923, 900, 889, 843, 809, 719, 676, 665, 656, 589, 572, 557, 549 $cm^{-1}$; MS-DCI ($NH_3$) *m*/*z* 320 (100, [M + $NH_4$]$^+$). A 94% ee and 50:50 *dl*/*meso* ratio was estimated for (*R*,*R*)-**5** from the chiral SFC analysis of the corresponding bis-1-naphthylcarbamate (*R*,*R*)-**16** (vide infra).

*(3S,14S)-Hexadeca-1,4,12,15-tetrayne-3,14-diol ((S,S)-**6a**).* Compound (*S*,*S*)-**6a** was obtained from (*R*,*R*)-**22a** as a viscous oil (75 mg, 80%) according to general procedure D: $R_f$ 0.3 (pentane/$Et_2O$, 1:1); $[\alpha]_D^{20}$ + 14 (*c* 0.7, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.32−1.46 (m, 4H), 1.46−1.61 (m, 4H), 2.23 (td, *J* 2.1, 7.0 Hz, 4H), 2.54 (m, 4H), 5.10 ppm (dt, *J* 2.2, 4.6 Hz, 2H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 18.5, 27.9, 28.1, 52.1, 72.2, 81.5, 85.8 ppm; IR (neat) $\nu$ 3267, 2945, 2842, 2298, 2216, 2122, 1485, 1455, 1416, 1332, 1322, 1318, 1294, 1119, 1008, 956, 934, 799, 758, 722, 685, 661, 578, 495 $cm^{-1}$; HRMS-DCI ($CH_4$) *m*/*z* [M − $H_2O$]$^+$ calcd for $C_{16}H_{17}O$ 225.1279, found 225.1284.

*(3R,14R)-Hexadeca-1,4,12,15-tetrayne-3,14-diol ((R,R)-**6a**).* Compound (*R*,*R*)-**6a** was obtained from (*S*,*S*)-**22a** as a viscous oil (70 mg, 75%) according to general procedure D. (*R*,*R*)-**6a** gave analytical data identical to that of its enantiomer except for its optical rotation. $[\alpha]_D^{20}$ −12 (*c* 0.7, $CHCl_3$).

*(3S,18S)-Icosa-1,4,16,19-tetrayne-3,18-diol ((S,S)-**6b**).* Compound (*S*,*S*)-**6b** was obtained from (*R*,*R*)-**22b** as a white powder (60 mg, 75%) according to general procedure D: $R_f$ 0.35 (pentane/$Et_2O$, 8:2); mp 54 °C; $[\alpha]_D^{20}$ − 5.0 (*c* 6.9, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.10−1.42 (m, 12H), 1.42−1.63 (m, 4H), 2.20 (td, *J* 2.1, 7.1 Hz, 4H), 2.53 (d, *J* 2.3 Hz, 2H), 2.58 (d, *J* 7.0 Hz, 2H), 2.09 (dd, *J* 2.0, 4.8 Hz, 2H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 18.7 (2C), 28.3 (2C), 28.8 (2C), 29.1 (2C), 29.4 (2C), 52.2 (2C), 72.3 (2C), 77.1 (2C), 81.6 (2C), 86.1 (2C) ppm; IR (neat) $\nu$ 3274, 2922, 2848, 2292, 2226, 2118, 1497, 1461, 1426, 1352, 1332, 1314, 1284, 1139, 1011, 976, 930, 797, 752, 724, 692, 659, 576, 499 $cm^{-1}$; HRMS-DCI ($CH_4$) *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{27}O_2$ 299.2011, found 299.2017. Selected crystal data for **6b**: $C_{20}H_{26}O_2$, *M* = 298.41, monoclinic, space group $P2_1$, *a* = 4.5889(2) Å, *b* = 46.758(2) Å, *c* = 8.8264(5) Å, *V* = 1829.68(15) Å$^3$, *Z* = 4, 12767 reflections collected (6915 independent, $R_{int}$ = 0.0312), *R* [$I > 2\sigma(I)$] = 0.1027, $wR^2$ [all data] = 0.2845, largest difference peak and hole = 0.390 and −0.407 e Å$^{-3}$.

*(3R,18R)-Icosa-1,4,16,19-tetrayne-3,18-diol ((R,R)-**6b**).* Compound (*R*,*R*)-**6b** was obtained as white powder (75 mg, 70%) from (*S*,*S*)-**22b** according to general procedure D. Compound (*R*,*R*)-**6b** gave analytical data identical to that of its enantiomer except for its optical rotation. $[\alpha]_D^{20}$ + 5.8 (*c* 7.1, $CHCl_3$).

*(3R,18S)-Icosa-1,4,16,19-tetrayne-3,18-diol (meso-**6b**).* Compound *meso*-**6b** was obtained as a white powder (50 mg, 70%) from *meso*-**22b** according to general procedure D: $R_f$ 0.35 (pentane/$Et_2O$, 8:2); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.28 (s, 8H), 1.37 (s, 4H), 1.52 (ddt, *J* 6.5, 7.5, 8.8 Hz, 4H), 2.18 (d, *J* 7.4 Hz, 2H), 2.23 (td, *J* 2.1, 7.1 Hz, 4H), 2.55 (d, *J* 2.3 Hz, 2H), 5.10 (dq, *J* 2.2, 7.5 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) $\delta$ 18.8 (2C), 28.4 (2C), 28.9 (2C), 29.2



DOI: 10.1021/acs.joc.5b00494
J. Org. Chem. 2015, 80, 5386−5394

(2C), 29.5 (2C), 52.4 (2C), 72.4 (2C), 77.1 (2C), 81.6 (2C), 86.3 (2C). IR (neat) $\nu$ 3271, 2926, 2842, 2293, 2224, 2119, 1494, 1465, 1428, 1351, 1335, 1312, 1281, 1135, 1013, 971, 929, 795, 754, 728, 694, 657, 578, 497 $cm^{-1}$; HRMS-DCI ($CH_4$) $m/z$ $[M + H]^+$ calcd for $C_{20}H_{27}O_2$ 299.2011, found 299.2015.

*(3S,4E)-1-[Tri(propan-2-yl)silyl]icos-4-en-1-yn-3-ol ((S)-**11**).* A mixture of (triisopropylsilyl)acetylene (**7**) (137 mg, 168 $\mu$L, 4 equiv) and $Et_2Zn$ (0.68 mL of a 1.1 M solution in toluene, 4 equiv) was held at reflux under $N_2$ atmosphere for 1 h before being cooled to rt. Then (*R*)-**9** (41 mg, 0.4 equiv) and Ti(O-*i*-Pr)$_4$ (53 mg, 1 equiv) in solution in anhydrous $Et_2O$ (2 mL) were added. After the mixture was stirred at rt for 1 h, **10** (50 mg, 0.19 mmol) was added in solution in anhydrous $Et_2O$ (1 mL), and the reaction was stirred at rt overnight. A saturated aqueous $NH_4Cl$ solution was added to the mixture before extraction with $Et_2O$. After standard treatment of the collected organic layers, the crude product was submitted to chromatography over $SiO_2$ (petroleum ether/$Et_2O$, 20:1) to give (*S*)-**11** (70 mg, 85%) as a colorless oil. The physical data and NMR spectra are in accord with those previously described in the literature.[11] A 81% ee was estimated for (*S*)-**11** on the basis of the chiral SFC analysis of the corresponding 1-naphthyl carbamate (*S*)-**12** (vide infra).

*(3S,4E)-1-[Tris(propan-2-yl)silyl]icos-4-en-1-yn-3-yl N-(Naphthalen-1-yl)carbamate ((S)-**12**).* Compound (*S*)-**12** (25 mg, 60%) was obtained as a yellow viscous solid from (*S*)-**11** according to general procedure A. The physical data and NMR spectra are in accord with those previously described in the literature.[11] Chiral SFC analysis: Chiralpak AD-H 5 $\mu$m (4.6 × 250 mm), SC $CO_2$ + 10% MeOH, 4 mL/min, 35 °C, 110 bar, UV 220 nm, $t_R$ (*R*) 7.5 min, $t_R$ (*S*) 4.7 min (see the Supporting Information).

*(2E,14E)-Hexadeca-2,14-dienedial (**13**).* To a solution of 1,12-dodecanedial[12b] (1 g, 5 mmol, 1 equiv) in toluene (80 mL) was added ethyl (triphenylphosphoranylidene)acetate (4.18 g, 12 mmol, 2.4 equiv), and the reaction mixture was heated to reflux for 6 h. The reaction mixture was cooled to rt, and toluene was evaporated under reduced pressure. The residue was cooled to 0 °C diluted with $Et_2O$ and the mixture filtered through a sintered glass funnel to remove the triphenylphosphinoxide. The organic layer was evaporated under reduced pressure to afford the crude product as a mixture of (*E,E*)/(*E,Z*)-isomers (9:1), which was purified by column chromatography (pentane/EtOAc, 9:1) to give 1,16-diethyl (2*E*,14*E*)-hexadeca-2,14-dienedioate (1.02 g, 60%) as a colorless liquid. The physical data and NMR spectra were in agreement with the literature.[24]

The bis-ester 1,16-diethyl (2*E*,14*E*)-hexadeca-2,14-dienedioate (1 g, 2.96 mmol, 1.0 equiv) was dissolved in $Et_2O$ (50 mL) and cooled to −78 °C. DIBAL-H (1 M solution in toluene) (14.8 mL, 14.8 mmol, 5 equiv) was added dropwise, and the reaction mixture was stirred at −78 °C for 4 h, before warming to rt, and further stirred for 1 h. The solution was cooled to 0 °C, quenched by the addition of a saturated solution of $NH_4Cl$ (10 mL), and warmed to rt with vigorous stirring over 1 h, producing a white precipitate. The precipitate was filtered through a pad of Celite and washed with $Et_2O$ (100 mL). The filtrate was then dried ($MgSO_4$) and concentrated in vacuo. Purification was carried out by flash column chromatography ($Et_2O$/PE, 2:1) to deliver product (2*E*,14*E*)-hexadeca-2,14-diene-1,16-diol (600 mg, 80%) as a white powder. The physical data and NMR spectra were in agreement with the literature.[25]

*(2E,14E)-16-Hydroxyhexadeca-2,14-dienal and (2E,14E)-hexadeca-2,14-dienedial **13**.* To a solution of (2*E*,14*E*)-hexadeca-2,14-diene-1,16-diol (1 g, 3.94 mmol) in DCM (50 mL) at 0 °C was added $MnO_2$ (2.27 g, 25.5 mmol) in one portion and the reaction mixture was stirred at rt until complete consumption of the starting diol (TLC monitoring, ca. 3−4 h). The $MnO_2$ was filtered off and the solvent was evaporated. Purification by flash chromatography (PE/$Et_2O$, 8:2) gave (2*E*,14*E*)-hexadeca-2,14-dienedial (**13**) (198 mg, 20% yield) and mono-oxidized compound (2*E*,14*E*)-16-hydroxyhexadeca-2,14-dienal-(690 mg, 70%). To a solution of the latter (500 mg, 1.98 mmol) in DCM (50 mL) at 0 °C was added PCC (1.28 g, 5.95 mmol, 3 equiv) in one portion, followed by silica (6 g) and the mixture was stirred at rt until complete consumption of the starting material (TLC monitoring 3−4 h). The precipitate was filtered through a pad of Celite and washed with DCM (20 mL). The filtrate was concentrated *in vacuo*. Purification by flash chromatography (PE/$Et_2O$ 8:2) gave **13** (395 mg, 80%) as a clear oil. The physical data and NMR spectra were in agreement to a previously described in literature.[12b]

*[(3R,18R)-3,18-dihydroxy-20-[tris(propan-2-yl)silyl]icosa-4,16-dien-1,19-diyn-1-yl]tris(propan-2-yl)silane ((R,R)-**14**).* A mixture of (triisopropylsilyl)acetylene (**7**) (360 $\mu$L, 1.6 mmol, 8 equiv) and $Et_2Zn$ (1.45 mL of a 1.1 M solution in toluene, 8 equiv) was held at reflux under $N_2$ atmosphere for 1 h before being cooled to rt. Then (*S*)-BINOL (45 mg, 0.8 equiv) and Ti(O-*i*-Pr)$_4$ (118 $\mu$L, 2 equiv) in solution in anhydrous $Et_2O$ (2 mL) were added. After the mixture was stirred at rt for 1 h, bis-enal **13** (50 mg, 0.2 mmol) in solution in anhydrous $Et_2O$ (1 mL) was added, and the reaction was allowed to stand with stirring at rt overnight. A saturated aqueous $NH_4Cl$ solution was added to the mixture, which was then extracted with $Et_2O$. After standard treatment of the collected organic layers the crude product was submitted to chromatography over $SiO_2$ (petroleum ether/$Et_2O$, 8:2) to give **14** as a colorless oil (74 mg, 60%): $R_f$ 0.3 (petroleum ether/$Et_2O$, 8:2); $[\alpha]_D^{20}$ − 28.0 (*c* 6.8, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.08 (s, 42H), 1.18−1.47 (m, 16H), 1.83 (s, 2H), 2.06 (q, *J* 6 Hz, 4H), 4.84 (d, *J* 6 Hz, 2H), 5.60 (ddt, *J* 1.4, 5.8, 15.3 Hz, 2H), 5.94 ppm (dtd, *J* 1.3, 6.8, 15.1 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.3 (6C), 18.7 (12C), 29.1 (2C), 29.2 (2C), 29.6 (2C), 29.7 (2C), 32.1 (2C), 63.5 (2C), 87 (2C), 107.1 (2C), 129.1 (2C), 134.3 (2C) ppm; IR (neat) $\nu$ 3600, 3314, 2924, 2893, 2864, 2757, 2724, 2247, 2170, 1728, 1668, 1462, 1383, 1366, 1302, 1244, 1088, 1074, 1017, 996, 965, 907, 882, 812, 733, 674, 659, 619, 578, 550 $cm^{-1}$; HRMS-DCI ($CH_4$) $m/z$ $[M + H]^+$ calcd for $C_{38}H_{71}O_2Si_2$ 615.4966, found 615.4993.

*(4E,16E)-18-{[(Naphthalen-1-yl)carbamoyl]oxy}-1,20-bis[tris(propan-2-yl)silyl]icosa-4,16-dien-1,19-diyn-3-yl N-(naphthalen-1-yl)carbamate ((R,R)-**15**).* Compound (*R,R*)-**15** (20 mg, 65%) was obtained as a yellow sticky solid from (*R,R*)-**14** according to general procedure A: $R_f$ 0.5 (petroleum ether/$Et_2O$, 8:2); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.10 (s, 21H), 1.35 (m, 8H), 2.00−2.17 (m, 2H), 5.65 (dd, *J* 6.2, 15.1 Hz, 1H), 5.91−6.04 (m, 1H), 6.13 (dt, *J* 6.8,14.3 Hz, 1H), 6.98 (s, 1H), 7.38−7.59 (m, 3H), 7.67 (d, *J* 8.2 Hz, 1H), 7.75−8.06 ppm (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.3, 18.8, 28.9, 29.3, 29.6, 29.8, 32.1, 66.2, 77.2, 88.8, 103.2, 120.6, 125.2, 125.3, 126.0, 126.1, 126.4, 128.9, 132.5, 134.2, 137.2, 153.3 ppm; IR (neat) $\nu$ 3336, 3227, 3053, 2925, 2863, 2177, 1842, 1709, 1647, 1598, 1580, 1534, 1495, 1463, 1403, 1382, 1366, 1346, 1258, 1206, 1176, 1100, 1067, 1027, 997, 964, 919, 882, 829, 790, 769, 730, 678, 566, 558, 529 $cm^{-1}$; HRMS-DCI ($CH_4$) $m/z$ $[M]^+$ calcd for $C_{60}H_{84}N_2O_4Si_2$ 952.5987, found 952.5970.

*(4E,16E)-18-{[(Naphthalen-1-yl)carbamoyl]oxy}icosa-4,16-dien-1,19-diyn-3-yl N-(Naphthalen-1-yl) Carbamate ((R,R)-**16**).* Compound (*R,R*)-**16** (15 mg, 60%) was obtained from (*R,R*)-**5** as yellow sticky solid according to general procedure A: $R_f$ 0.3 (pentane/$Et_2O$, 3:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.21−1.32 (m, 8H), 1.42−1.49 (m, 2H), 2.12 (q, *J* 7.1 Hz, 1H), 2.66 (d, *J* 2.2 Hz, 1H), 5.66 (dd, *J* 6.8, 15.0 Hz, 1H), 5.97 (ddd, *J* 1.1, 2.2, 6.3 Hz,1H), 6.12 (dd, *J* 6.8, 15.3 Hz, 1H), 7.03 (s, 1H), 7.49−7.55 (m, 3H), 7.69 (d, *J* 8.2 Hz, 1H), 7.94−7.89 ppm (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) $\delta$ 28.6, 29.2, 29.4, 29.5, 29.7, 32.0, 65.4, 75.1, 77.2, 80.0, 120.3, 124.5, 125.1, 125.8, 126.0, 126.3, 128.8, 132.2, 134.1, 137.5, 152.9 ppm; IR (neat) $\nu$ 3297, 3051, 2924, 2852, 2124, 1712, 1629, 1598, 1578, 1536, 1496, 1465, 1437, 1402, 1373, 1346, 1256, 1207, 1176, 1100, 1068, 1026, 1000, 964, 874, 791, 769, 731, 665, 639, 571, 489 $cm^{-1}$; HRMS-DCI ($CH_4$) $m/z$ $[M-H]^+$ calcd for $C_{42}H_{45}N_2O_4$ 641.3379, found 641.3400. Chiral SFC analysis: Chiralpak IA-3 (4.6 × 100 mm), SC $CO_2$ + 25% MeOH, 2.7 mL/min, 40 °C, 130 bar, UV 220 nm, $t_R$ 14.99 (*R,R*), 17.13 (*meso*) and 18.71 (*S,S*) min (see the Supporting Information).

*Tetradeca-1, 13-diyne (**17b**).* To a solution of **20** (2.0 g, 5.99 mmol) in a mixture of THF/MeOH (1:1) (100 mL) at 0 °C was added $K_2CO_3$ (4.95 g, 35.9 mmol, 6 equiv) in one portion. The reaction mixture was stirred at rt overnight, then diluted with a saturated aqueous $NH_4Cl$ solution (200 mL) and extracted with $Et_2O$. The combined organic layers were washed with brine and dried with $Na_2SO_4$. The crude product was recrystallized from ethanol to give



DOI: 10.1021/acs.joc.5b00494
J. Org. Chem. 2015, 80, 5386−5394

diyne **17b** (910 mg, 80%) as a white powder. The physical data and NMR spectra were in agreement with the literature.[26]

*1,10-Dibromodecane (**19**).* Compound **19** was obtained (5.0 g, 80%) by reaction of diol **18** with HBr at 100 °C according to a previously described procedure.[27]

*1,14-Bis(trimethylsilyl)tetradeca-1, 13-diyne (**20**).* Trimethylsilylacetylene (6.56 g, 0.0668 mol, 4.0 equiv) was dissolved in THF (100 mL) and cooled to −78 °C. To this solution was added dropwise *n*-BuLi (27 mL of 2.5 M solution in hexanes, 0.0668 mol, 4.0 equiv). The reaction mixture was stirred at −78 °C for 30 min and then warmed to 0 °C for 50 min. The anion obtained was transferred by cannula to a solution of dibromide **19** (5 g, 0.0167 mol, 1.0 equiv) in THF (50 mL) at rt. Freshly distilled HMPA (48 g, 0.267 mol, 16.0 equiv) was then added, and the brown reaction mixture was stirred at rt for 12 h before being quenched with 3 N HCl. The aqueous layer was extracted with $Et_2O$, and the organic layer was separated and washed sequentially with saturated $NaHCO_3$ and brine. Then the combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on $SiO_2$ (pentane) to give **20** (4.2 g, 75%). The physical data and NMR spectra are in accordance with the literature.[27]

*[(3S,14S)-3,14-Dihydroxy-16-(trimethylsilyl)hexadeca-1,4,12,15-tetrayn-1-yl]trimethylsilane ((S,S)-**22a**).* Compound (*S*,*S*)-**22a** was obtained from **17a** and **21** as a colorless oil (358 mg, 90%) according to general procedure C using (+)-*N*-methylephedrine: $R_f$ 0.3 (pentane/$Et_2O$, 8:2); $[\alpha]_D^{20}$ − 1.75 (*c* 2.3, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.19 (s, 18H), 1.40−1.47 (m, 4H), 1.51−1.60 (m, 4H), 2.17 (d, *J* 6 Hz, 2H), 2.26 (td, *J* 2.1, 7 Hz, 4H), 5.12 ppm (dt, *J* 2.1, 7.3 Hz, 2H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ −0.17 (6C), 18.7 (2C), 28.1 (2C), 28.3 (2C), 52.8 (2C), 77.6 (2C), 85.6 (2C), 88.9 (2C), 102.7 (2C) ppm; IR (neat) $\nu$ 3328, 3276, 2931, 2852, 2682, 2351, 2292, 2226, 2120, 1630, 1498, 1461, 1426, 1359, 1305, 1293, 1207, 1139, 1018, 933, 796, 692, 667, 604, 540, 518, 462 cm$^{-1}$; HRMS-DCI ($CH_4$) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{34}O_2Si_2$ 386.2097, found 386.2080. A 78% ee and a 62:38 *dl*/*meso* ratio was estimated for (*S*,*S*)-**22a** from the chiral SFC analysis of the corresponding bis-1-naphthylcarbamate (*S*,*S*)-**23a** (vide infra).

*[(3R,14R)-3,14-Dihydroxy-16-(trimethylsilyl)hexadeca-1,4,12,15-tetrayn-1-yl]trimethylsilane ((R,R)-**22a**).* The compound (*R*,*R*)-**22a** was obtained from **17a** and **21** as a colorless oil (273 mg, 85%) according to general procedure C using (−)-*N*-methylephedrine. Compound **22a** gave analytical data identical to that of its enantiomer except for optical rotation. $[\alpha]_D^{20}$ + 1.68 (*c* 2.6, $CHCl_3$).

*[(3R,18R)-3,18-Dihydroxy-20-(trimethylsilyl)icosa-1,4,16,19-tetrayn-1-yl]trimethylsilane ((R,R)-**22b**).* Compound (*R*,*R*)-**22b** was obtained from **17b** and **21** as a colorless oil (197 mg, 85%) according to general procedure C using (−)-*N*-methylephedrine. $R_f$ 0.3 (pentane/$Et_2O$, 8:2); $[\alpha]_D^{20}$ + 1.76 (*c* 1.8, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.18 (s, 18H), 1.44−1.18 (m, 12H), 1.60−1.44 (m, 4H), 2.21 (td, *J* 7.1, 2.1 Hz, 4H), 2.29 (d, *J* 7.2 Hz, 2H), 5.09 ppm (dt, *J* 7.1, 2.1 Hz, 2H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ − 0.2 (6C), 18.9 (2C), 28.4 (2C), 28.9 (2C), 29.2 (2C), 29.5 (2C), 52.9 (2C), 77.4 (2C), 85.9 (2C), 88.9 (2C), 102.7 (2C) ppm; IR (neat) $\nu$ 3516, 3000, 2928, 2855, 2654, 2291, 2232, 2177, 1950, 1707, 1627, 1463, 1429, 1408, 1369, 1328, 1295, 1249, 1141, 1029, 962, 839, 759, 737, 700, 668, 647, 617, 593, 573, 506 cm$^{-1}$; HRMS-DCI ($CH_4$) *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{42}O_2Si_2$ 442.2721, found 442.2723. A 76% ee and 77:23 *dl*/*meso* ratio was estimated for (*R*,*R*)-**22b** from the chiral SFC analysis of the corresponding naphthyl carbamate (*R*,*R*)-**23b** (vide infra).

*[(3S,18S)-3,18-Dihydroxy-20-(trimethylsilyl)icosa-1,4,16,19-tetrayn-1-yl]trimethylsilane ((S,S)-**22b**).* Compound (*S*,*S*)-**22b** was obtained as a colorless oil (190 mg, 80%) according to general procedure C using (+)-*N*-methylephedrine. (*S*,*S*)-**22b** gave analytical data identical to that of its enantiomer except for optical rotation. $[\alpha]_D^{20}$ −1.6 (*c* 1.3, $CHCl_3$). A 87% ee and 90:10 *dl*/*meso* ratio was estimated for (*S*,*S*)-**22b** from the chiral SFC analysis of the corresponding bis-1-naphthylcarbamate (*S*,*S*)-**23b** (vide infra).

*[(3R,18S)-3,18-Dihydroxy-20-(trimethylsilyl)icosa-1,4,16,19-tetrayn-1-yl]trimethylsilane (meso-**22b**).* A 25 mL flask was charged with $Zn(OTf)_2$ (920 mg, 2.53 mmol, 8 equiv) and (+)-*N*-methylephedrine (453 mg, 2.53 mmol, 8 equiv) and purged with dry argon for 15 min. To the flask were added anhydrous $CH_2Cl_2$ (10 mL) and triethylamine (256 mg, 2.53 mmol, 8 equiv). The resulting mixture was vigorously stirred for 2 h at rt. Then alkyne (*R*)-**24** (100 mg, 0.36 mmol, 1 equiv, solution in dried $CH_2Cl_2$) was introduced by syringe in one portion. After another 1 h of stirring the 3-(trimethylsilyl)propiolaldehyde (**21**) (160 mg, 1.24 mmol, 4 equiv) was added and the mixture was stirred at rt overnight. A saturated aqueous $NH_4Cl$ solution was added, and the mixture was extracted with $CH_2Cl_2$. After standard treatment of the collected organic layers, the crude product was submitted to chromatography over $SiO_2$ (pentane/$Et_2O$, 8:2) to give a colorless oil *meso*-**22b** (100 mg, 70%): $R_f$ 0.35 (pentane/$Et_2O$, 8:2); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.19 (s, 18H), 1.18−1.42 (m, 12H), 1.45−1.61 (m, 4H), 2.15 (d, *J* 7.2 Hz, 2H), 2.22 (td, *J* 2.1, 7.2 Hz, 4H), 5.09 (dt, *J* 2.0, 7.2 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) $\delta$ −0.1 (6C), 18.9 (2C), 28.4 (2C), 29.0 (2C), 29.2 (2C), 29.6 (2C), 52.9 (2C), 77.4 (2C), 86.0 (2C), 89.0 (2C), 102.7 (2C). IR (neat) $\nu$ 3520, 3006, 2925, 2860, 2652, 2289, 2229, 2175, 1953, 1709, 1624, 1460, 1425, 1410, 1363, 1320, 1298, 1253, 1146, 1024, 959, 841, 750, 732, 708, 660, 641, 611, 599, 569, 509 cm$^{-1}$; HRMS-ES *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{42}O_2Si_2Na$ 465.2621, found 465.2617. A 89:11 *meso*/*dl* ratio was estimated for *meso*-**22b** on the basis of the chiral SFC analysis of the corresponding bis-1-naphthyl carbamate *meso*-**23b** (vide infra).

*14-{[(Naphthalen-1-yl)carbamoyl]oxy}-1,16-bis(trimethylsilyl)-hexadeca-1,4,12,15-tetrayn-3-yl N-(Naphthalen-1-yl) Carbamate ((S,S)-**23a**).* Compound (*S*,*S*)-**23a** was obtained from **22a** as a yellow semisolid (30 mg, 65%) according to general procedure A: $R_f$ 0.4 (petroleum ether/$Et_2O$, 8:2); $^1$H NMR (404 MHz, $CDCl_3$) $\delta$ 0.23 (s, 18H), 1.40−1.50 (m, 4H), 1.52−1.60 (m, 4H), 2.28 (td, *J* 2.1, 6.8 Hz, 4H), 6.20 (td, *J* 2.1, 1.3 Hz, 2H), 7.10 (s, 2H), 7.44−7.59 (m, 6H), 7.65−7.75 (m, 2H), 7.83−7.96 ppm (m, 6H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) $\delta$ − 0.3 (6C), 18.7 (2C), 27.9 (2C), 28.2 (2C), 55.1 (2C), 74.5 (2C), 86.8 (2C), 90.4 (2C), 98.9 (2C), 120.3, 125.2, 125.9, 126.0, 126.3, 128.8, 132.0, 134.0, 152.4 (2C) ppm; IR (neat) $\nu$ 3328, 3053, 2935, 2859, 2308, 2243, 2186, 1931, 1714, 1629, 1598, 1579, 1537, 1496, 1463, 1437, 1403, 1372, 1346, 1308, 1291, 1250, 1204, 1175, 1155, 1098, 1067, 1029, 996, 953, 909, 843, 791, 760, 731, 702, 657, 641, 629, 608, 563, 548 cm$^{-1}$; HRMS-DCI ($CH_4$) *m*/*z* [M + H]$^+$ calcd for $C_{44}H_{48}N_2O_4Si_2$ 724.3153, found 724.3181. Chiral SFC analysis: Chiralpak AD-H 5 $\mu$m (4.6 × 250 mm), SC $CO_2$ + 20% MeOH, 4 mL/min, 35 °C, 110 bar, UV 220 nm, $t_R$ 7.22 (*S*,*S*), 9.02 (*meso*) and 10.5 (*R*,*R*) min (see the Supporting Information).

*18-{[(Naphthalen-1-yl)carbamoyl]oxy}-1,20-bis(trimethylsilyl)-icosa-1,4,16,19-tetrayn-3-yl N-(Naphthalen-1-yl) Carbamate ((R,R)-**23b**).* Compound (*R*,*R*)-**23b** was obtained from **22b** as a yellow waxy solid (25 mg, 50%) according to general procedure A: $R_f$ 0.4 (petroleum ether/$Et_2O$, 8:2); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.24 (s, 18H), 1.23−1.44 (m, 12H), 1.44-1.60 (m, 4H), 2.25 (td, *J* 7.1, 2.1 Hz, 4H), 6.19 (t, *J* 2.1 Hz, 2H), 7.07 (s, 2H), 7.41-7.57 (m, 6H), 7.62−7.74 (m, 2H), 7.80−8.00 ppm (m, 6H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ − 0.2, 19.0, 28.3, 29.0, 29.2, 29.6, 55.3, 74.5, 87.2, 90.6, 99.1, 120.4, 125.4, 125.9, 126.2, 126.5, 128.9, 132.2, 134.2, 152.5 ppm; IR (neat) $\nu$ 3301, 3060, 2958, 2928, 2855, 2242, 2186, 1943, 1732, 1699, 1659, 1630, 1599, 1551, 1504, 1465, 1435, 1405, 1393, 1374, 1346, 1304, 1275, 1246, 1198, 1177, 1164, 1119, 1101, 1067, 1027, 996, 954, 932, 902, 843, 792, 770, 732, 712, 701, 650, 590, 561 cm$^{-1}$; HRMS-DCI ($CH_4$) *m*/*z* [M-Si($CH_3$)$_3$]$^+$ calcd for $C_{45}H_{47}N_2O_4Si$: 707.3305, found 707.3307. Chiral SFC analysis: Chiralpak IC 3 $\mu$m (4.6 × 100 mm), SC $CO_2$ + 20% MeOH, 2.5 mL/min, 35 °C, 130 bar, UV 220 nm, $t_R$ 9.45 (*S*,*S*), 9.68 (*meso*) and 9.89 (*R*,*R*) min (see the Supporting Information).

*18-{[(Naphthalen-1-yl)carbamoyl]oxy}-1,20-bis(trimethylsilyl)-icosa-1,4,16,19-tetrayn-3-yl N-(Naphthalen-1-yl) Carbamate (meso-**23b**).* Compound *meso*-**23b** was obtained as a yellow waxy solid (25 mg, 50%) according to general procedure A: $R_f$ 0.4 (petroleum ether/$Et_2O$, 8:2); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.22 (s, 18H), 1.25 (s, 8H), 1.36 (m, 4H), 1.48−1.60 (m, 4H), 2.25 (td, *J* 2.1, 7.1 Hz, 4H), 6.19 (br.s, 2H), 7.08 (s, 2H), 7.52 (s, 6H), 7.68 (d, *J* 8.5



DOI: 10.1021/acs.joc.5b00494
J. Org. Chem. 2015, 80, 5386−5394

Hz, 2H), 7.83−7.96 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) $\delta$ −0.2 (6C), 19.0 (2C), 28.3 (2C), 29.0 (2C), 29.2 (2C), 29.6 (2C), 55.3 (2C), 74.5 (2C), 87.2 (2C), 90.6 (2C), 99.1 (2C), 120.4, 125.4, 125.9, 126.2, 126.5, 128.9, 132.2, 134.2, 152.5 (2C); IR (neat) $\nu$ 3306, 3058, 2956, 2926, 2858, 2244, 2183, 1946, 1731, 1695, 1655, 1631, 1594, 1550, 1508, 1469, 1431, 1408, 1391, 1376, 1341, 1308, 1271, 1242, 1195, 1172, 1161, 1113, 1109, 1061, 1022, 998, 951, 936, 901, 845, 796, 771, 731, 711, 705, 656, 594, 563 $cm^{-1}$; HRMS-ES $m/z$ $[M + Na]^+$ calcd for $C_{48}H_{56}N_2O_4NaSi_2$: 803.3676, found 803.3683. Chiral SFC analysis: Chiralpak IC-3 (4.6 × 100 mm), SC $CO_2$ + 20% MeOH, 2.5 mL/min, 35 °C, 130 bar, UV 220 nm, $t_R$ 9.45 (*S,S*), 9.68 (*meso*) and 9.89 (*R,R*) min (see the Supporting Information).

*(3R)-1-(Trimethylsilyl)heptadeca-1,4,16-triyn-3-ol ((R)-**24**).* A 25 mL flask was charged with $Zn(OTf)_2$ (765 mg, 2.104 mmol, 4 equiv) and (−)-*N*-methylephedrine (377 mg, 2.104 mmol, 4 equiv) and purged with dry argon for 15 min. To the flask were added anhydrous $CH_2Cl_2$ (15 mL) and triethylamine (212 mg, 2.104 mmol, 4 equiv). The resulting mixture was vigorously stirred for 2 h at rt. Then the bis-alkyne **17b** (100 mg, 0.526 mmol, 1 equiv, solution in anhydrous $CH_2Cl_2$) was introduced by syringe in one portion. After another 1 h of stirring, the 3-(trimethylsilyl)propiolaldehyde (**21**) (66 mg, 0.526 mmol, 1 equiv) was added, and then the mixture was stirred at rt overnight. A saturated aqueous $NH_4Cl$ solution was added, and the mixture was extracted with $CH_2Cl_2$ (3 × 10 mL). After standard treatment of the gathered organic layers, the crude product was submitted to chromatography over $SiO_2$ (pentane/$Et_2O$, 9:1) to give compound (*R*)-**24** (85%, 140 mg): $R_f$ 0.35 (pentane/$Et_2O$, 9:1); $[\alpha]_D^{20}$ − 3.2 (*c* 5.8, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.18 (s, 9H), 1.17−1.44 (m, 12H), 1.51 (pseudo q, *J* 8.4 Hz, 4H), 1.94 (t, *J* 2.6 Hz, 1H), 2.09−2.27 (m, 4H), 2.38 (d, *J* 7.1 Hz, 1H), 5.09 ppm (dt, *J* 7.1, 2.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ − 0.2, 18.5, 18.8, 28.4, 28.6, 28.8, 28.9, 29.2, 29.5 (2C), 52.8, 68.2, 77.2, 77.4, 84.8, 85.8, 88.8, 102.7 ppm; IR (neat) $\nu$ 3310, 2927, 2855, 2290, 2232, 2177, 2117, 1464, 1431, 1370, 1328, 1295, 1249, 1141, 1030, 961, 841, 760, 721, 700, 622, 574, 559 $cm^{-1}$; HRMS-DCI ($CH_4$) $m/z$ $[M + H]^+$ calcd for $C_{20}H_{33}OSi$ 317.2301, found 317.2310. A 95% ee was estimated for (*R*)-**24** from chiral SFC analysis of the corresponding 1-naphthyl carbamate (*R*)-**25** (vide infra).

*1-(Trimethylsilyl)heptadeca-1,4,16-triyn-3-yl N-(Naphthalen-1-yl) Carbamate ((R)-**25**).* Compound (*R*)-**25** was obtained from (*R*)-**24** as a yellow sticky solid (20 mg, 50%) according to general procedure C: $R_f$ 0.3 (petroleum ether/$Et_2O$, 10:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.24 (s, 9H), 1.20−1.45 (m, 12H), 1.45−1.62 (m, 4H), 1.96 (t, *J* 2.7 Hz, 1H), 2.19 (td, *J* 2.6, 7.0 Hz, 2H), 2.28 (td, *J* 2.1, 7.1 Hz, 2H), 6.21 (t, *J* 2.1 Hz, 1H), 7.11 (s, 1H), 7.62−7.44 (m, 3H), 7.70 (d, *J* 8.5 Hz, 1H), 7.83−8.12 ppm (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ − 0.3, 18.4, 18.8, 28.2, 28.5, 28.8, 28.9, 29.1, 29.5, 55.2, 68.1, 74.4, 84.8, 87.1, 90.4, 99.0, 120.3, 125.2, 125.8, 126.1, 126.3, 128.8, 132.1, 134.1, 152.4 ppm; IR (neat) $\nu$ 3320, 3022, 2932, 2841, 2130, 1720, 1619, 1588, 1588, 1526, 1476, 1452, 1417, 1415, 1385, 1325, 1261, 1203, 1155, 1123, 1028, 1016, 1010, 952, 884, 785, 763, 741, 644, 631, 551 $cm^{-1}$; HRMS-DCI ($CH_4$) $m/z$ $[M - H]^+$ calcd for $C_{31}H_{40}NO_2Si$ 486.2828, found 486.2832. Chiral SFC analysis: Chiralpak AD-H 5 $\mu$m (4.6 × 250 mm), SC $CO_2$ + 10% MeOH, 4 mL/min, 40 °C, 150 bar, UV 220 nm, $t_R$ 4.05 (*S*) et 5.47 (*R*) min (see the Supporting Information).

## ■ ASSOCIATED CONTENT

### Supporting Information

[Stereoisomeric ratio calculation for compound **14**. $^1H$ and $^{13}C\{^1H\}$ NMR spectra for (*R,R*)-**5**, (*S,S*)-**6a**, (*S,S*)-**6b**, *meso*-**6b**, (*R,R*)-**14**, (*R,R*)-**15**, (*R,R*)-**16**, (*R,R*)-**22a**, (*R,R*)-**22b**, *meso*-**22b**, (*S,S*)-**23a**, (*R,R*)-**23b**, *meso*-**23b**, (*R*)-**24**, and (*R*)-**25**. Crystallographic data and CIF for compounds **12** and **6b**. SFC chiral chromatograms for (*S*)-**12**, a stereoisomeric mixture of **16**, (***R,R***)-**16**, a stereoisomeric mixture of **23a**, (***S,S***)-**23a**, a stereoisomeric mixture of **23b**, (*R,R*)-**23b**, (*S,S*)-**23b**, *meso*-**23b**, an enantiomeric mixture of **25**, and (*R*)-**25**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00494.

## ■ AUTHOR INFORMATION


### Corresponding Authors

*Fax: (+33)5 61 55 30 03. E-mail: valerie.maraval@lcc-toulouse.fr.

*Fax: (+33)5 61 55 30 03. E-mail: chauvin@lcc-toulouse.fr.

*Fax: (+33)5 61 55 60 11. E-mail: genisson@chimie.ups-tlse.fr.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

D.L. was supported by the French Embassy in Kiev, Ukraine, and the investigations were performed within the framework of the "Groupement Franco-Ukrainien en Chimie Moléculaire" (GDRI) funded by the "Centre National de la Recherche Scientifique" (CNRS). The French Embassy in Kiev and the CNRS are thus acknowledged. R.C. is also indebted to the CNRS for half of a teaching sabbatical in 2014−2015. The "Institut de Chimie de Toulouse" (ICT) and the "Plateforme Intégrée de Criblage Toulousaine" (PICT) are acknowledged for SFC facilities. We are thankful to the "Institut des Technologies Avancées en sciences du Vivant" (ITAV) for biological evaluations.

## ■ REFERENCES


(1) (a) Dembitsky, V. M. *Lipids* **2006**, *41*, 883−924. (b) Dembitsky, V. M.; Levitsky, D. O.; Gloriozova, T. A.; Poroikov, V. V. *Nat. Prod. Commun.* **2006**, *1*, 773−811.

(2) Listunov, D.; Maraval, D.; Chauvin, R.; Génisson, Y. *Nat. Prod. Rep.* **2015**, *32*, 49−75.

(3) (a) Fusetani, N.; Kato, Y.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1983**, *24*, 2771−2774. (b) Fusetani, N.; Shiragaki, T.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1987**, *28*, 4313−4314. (c) Isaacs, S.; Kashman, Y.; Loya, S.; Hizi, A.; Loya, Y. *Tetrahedron* **1993**, *49*, 10435−10438.

(4) (a) Higa, T.; Tanaka, J.; Kitamura, A.; Koyama, T.; Takahashi, M.; Uchida, T. *Pure Appl. Chem.* **1994**, *66*, 2227−2230. (b) Kobayashi, M.; Mahmud, T.; Tajima, H.; Wang, W. Q.; Aoki, S.; Nakagawa, S.; Mayumi, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1996**, *44*, 720−724.

(5) (a) Seo, Y.; Cho, K. W.; Rho, J. R.; Shin, J.; Sim, C. J. *Tetrahedron* **1998**, *54*, 447−462. (b) Kim, J. S.; Im, K. S.; Jung, J. H.; Kim, Y. L.; Kim, J.; Shim, C. J.; Lee, C. O. *Tetrahedron* **1998**, *54*, 3151−3158.

(6) (a) Wright, A. E.; Mcconnell, O. J.; Kohmoto, S.; Lui, M. S.; Thompson, W.; Snader, K. M. *Tetrahedron Lett.* **1987**, *28*, 1377−1380. (b) Hitora, Y.; Takada, K.; Okada, S.; Ise, Y.; Matsunaga, S. *J. Nat. Prod.* **2011**, *74*, 1262−1267.

(7) Ortega, M. J.; Zubia, E.; Carballo, J. L.; Salva, J. *J. Nat. Prod.* **1996**, *59*, 1069−1071.

(8) (a) For dideoxypetrosynol A, see: Choi, H. J.; Bae, S. J.; Kim, N. D.; Jung, J. H.; Choi, Y. H. *Int. J. Mol. Med.* **2004**, *14*, 1091−1096. (b) For petrotetrayndiol, see: Choi, H. J.; Yee, S. B.; Park, S. E.; Im, E.; Jung, J. H.; Chung, H. Y.; Choi, Y. H.; Kim, N. D. *Cancer Lett.* **2006**, *232*, 214−225. (c) For (3*S*)-icos-(4*E*)-en-1-yn-3-ol and (3*S*)-14-methyldocos-(4*E*)-en-1-yn-3-ol, see: Zovko, A.; Viktorsson, K.; Haag, P.; Kovalerchick, D.; Farnegardh, K.; Alimonti, A.; Ilan, M.; Carmeli, S.; Lewensohn, R. *Mol. Cancer Ther.* **2014**, *13*, 2941−2954.

(9) For other another review on the synthetic approaches to acetylenic lipids, see: Gung, B. W. *C. R. Chim.* **2009**, *12*, 489−505.

(10) (a) Zhou, G.-X.; Molinski, T. F. *Mar. Drugs* **2003**, *1*, 46−53. (b) Izumi, M.; Yogosawa, S.; Aoki, S.; Watanabe, H.; Kamiyama, J.; Takahara, Y.; Sowa, Y.; Kobayashi, M.; Hosoi, H.; Sugimoto, T.; Sakai, T. *Int. J. Oncol.* **2006**, *29*, 169−173.




DOI: 10.1021/acs.joc.5b00494
*J. Org. Chem.* 2015, 80, 5386−5394

(11) El Arfaoui, D.; Listunov, D.; Fabing, I.; Oukessou, M.; Frongia, C.; Lobjois, V.; Samson, A.; Ausseil, F.; Ben-Tama, A.; El Hadrami, E.; Chauvin, R.; Génisson, Y. *ChemMedChem* **2013**, *8*, 1779−1786.
(12) (a) Braekman, J. C.; Daloze, D.; Devijver, C.; Dubut, D.; van Soest, R. W. M. *J. Nat. Prod.* **2003**, *66*, 871−872. (b) Shirouzu, T.; Watari, K.; Ono, M.; Koizumi, K.; Saiki, I.; Tanaka, C.; van Soest, R. W. M.; Miyamoto, T. *J. Nat. Prod.* **2013**, *76*, 1337−1342.
(13) For a recent review on the methods of enantioselective addition of alkynes to carbonyl groups, see: Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963−983.
(14) (a) Trost, B. M.; Weiss, A. H.; Jacobi von Wangelin, A. *J. Am. Chem. Soc.* **2006**, *128*, 8−9. (b) Trost, B. M.; Bartlett, M. J.; Weiss, A. H.; Jacobi von Wangelin, A.; Chan, V. S. *Chem.—Eur. J.* **2012**, *18*, 16498−16509.
(15) Trost, B. M.; Weiss, A. H. *Org. Lett.* **2006**, *8*, 4461−4464.
(16) (a) Gao, G.; Moore, D.; Xie, R. G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143−4146. (b) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855−1857. (c) For a recent review article, see: Pu, L. *Acc. Chem. Res.* **2014**, *47*, 1523−1535.
(17) For isolation, see: (a) Gunasekera, S. P.; Faircloth, G. T. *J. Org. Chem.* **1990**, *55*, 6223−6225. (b) Aiello, A.; Fattorusso, E.; Menna, M. *J. Nat. Prod.* **1992**, *55*, 1275−1280. (c) Hallock, Y. F.; Cardellina, J. H.; Blaschak, M. S.; Alexander, M. R.; Prather, T. R.; Shoemaker, R. H.; Boyd, M. R. *J. Nat. Prod.* **1995**, *58*, 1801−1807. For previous syntheses, see: (d) Gung, B. W.; Dickson, H. D.; Seggerson, S.; Bluhm, K. *Synth. Commun.* **2002**, *32*, 2733−2740. (e) Li, Z. Y.; Wang, M.; Bian, Q. H.; Zheng, B.; Mao, J. Y.; Li, S. N.; Liu, S. Z.; Wang, M. A.; Zhong, J. C.; Guo, H. C. *Chem.—Eur. J.* **2011**, *17*, 5782−5786. (f) Sharma, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **1998**, *9*, 2635−2639. (g) Morishita, K.; Kamezawa, M.; Ohtani, T.; Tachibana, H.; Kawase, M.; Kishimoto, M.; Naoshima, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 513−518. (h) Garcia, J.; Lopez, M.; Romeu, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2617−2626. (i) Lu, W.; Zheng, G. R.; Cai, J. C. *Tetrahedron* **1999**, *55*, 4649−4654.
(18) Mouhtady, O.; Gaspard-Iloughmane, H.; Laporterie, A.; Le Roux, C. *Tetrahedron Lett.* **2006**, *47*, 4125−4128.
(19) For the recent report of BINOL-3,3′-triflone phosphoramidites, see: Kruck, M.; Paz Munoz, M.; Bishop, H. L.; Frost, C. G.; Chapman, C. J.; Kociok-Köhn, G.; Butts, C. P.; Lloyd-Jones, G. C. *Chem.−Eur. J.* **2008**, *14*, 7808−7812.
(20) CCDC-1046514 contains the supplementary crystallographic data for compound **12**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.a-c.uk/data_request/cif.
(21) Mori, K.; Akasaka, K.; Matsunaga, S. *Tetrahedron* **2014**, *70*, 392−401.
(22) (a) Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373−381 and references cited therein. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688. (c) Carreira, E. M. *Chimia* **2001**, *55*, 818−820. (d) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605−2606.
(23) CCDC-1046515 contains the supplementary crystallographic data for compound **6b**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.a-c.uk/data_request/cif.
(24) Outram, H. S.; Raw, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2002**, *43*, 6185−6187.
(25) Iriye, R.; Toya, T.; Makin, J.; Aruga, R.; Doi, Y.; Handa, S.; Tanaka, H. *Agric. Biol. Chem.* **1988**, *52*, 989−996.
(26) Huang, J.; Wang, H.; Wu, C.; Wulff, W. D. *Org. Lett.* **2007**, *9*, 2799−2802.
(27) De, S.; Aswal, V. K.; Ramakrishnan, S. *Langmuir* **2010**, *26*, 17882−17889.



DOI: 10.1021/acs.joc.5b00494
*J. Org. Chem.* 2015, 80, 5386−5394