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Synthesis of the Landomycinone Skeleton

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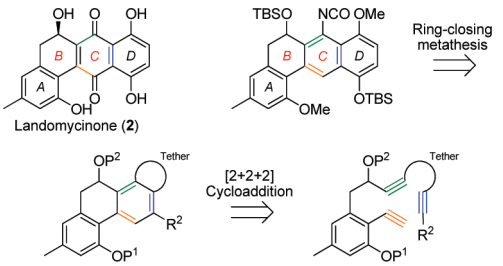

The synthesis of the highly functionalized tetracyclic skeleton of landomycinone (**2**), the aglycon of landomycins, was performed using two pivotal steps relying on metal-catalyzed reactions. They are (1) a [2 + 2 + 2] cycloaddition of alkynes promoted by Wilkinson's catalyst to build rings B and C concomitantly and (2) a ring-closing metathesis followed by aromatization to build ring D.

1. Introduction

Landomycin A (**1**) (Figure 1) was isolated in 1990 and identified as the main bioactive compound extracted from a broth of the actinobacteria *Streptomyces cyanogenus* (strain S136, DSM 5087).[1] The aglycon core of this glycosidic antibiotic is an angular tetracyclic decaketide named landomycinone (**2**), which is bonded to the hexasaccharidic chain at a phenolic position. Three related compounds featuring altered oligosaccharidic side chains, named landomycins B−D, were isolated in lower amounts from the same fermentation experiments. Landomycins D and E were isolated from another actinobacteria named *Streptomyces globisporum* (strain 1912).[2]

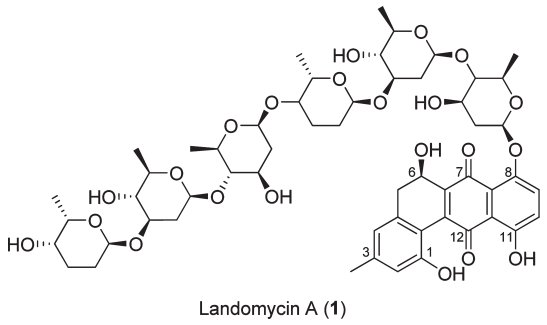

FIGURE 1. Landomycin A (**1**).

All landomycins contain the same aglycon, but the length of their oligosaccharidic side chain (two to six sugars) is variable. They belong to the large family of angucycline antibiotics, this name reflecting the angular geometry of their aglycon skeleton.[2,3] A large number of genetic engineering studies were conducted in order to understand the biosynthesis of landomycins and resulted in the production of many new related compounds possessing structural modifications on both the aglycon and/or the oligosaccharide.[4]

All landomycins, as well as landomycinone (**2**), are endowed with diverse biological activities, but their marked

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antitumor properties are of particular interest.[5] Landomycin A (**1**) is the most cytostatic member of the family and exhibits activity on cells comparable with clinically used anticancer agents such as bleomycin, cisplatin, doxorubicin, or paclitaxel.[5] One must notice that even multidrug-resistant cell lines remain sensitive to these compounds.[7] Studies of its mode of action demonstrated that landomycin A (**1**) inhibits DNA synthesis and cell cycle progression at the G_1/S phase.[6] Landomycin E has the same effect on DNA synthesis but without any modification of cell cycle[7] and seems to induce cell death via depolarization of the membrane of mitochondria.

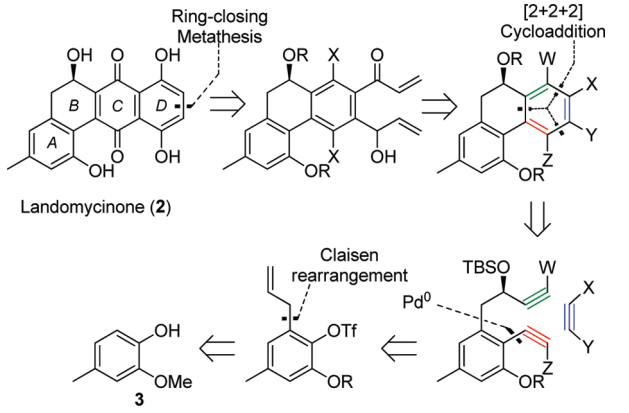
While the syntheses of some of the oligosaccharidic chains or of the landomycinone (**2**) have been reported,[8] to date there is no total synthesis of any member of this family. The first study of the aglycon synthesis consisted of the biomimetic preparation of a putative biosynthetic intermediate via a base-triggered double cyclization to form rings A and B.[9] In 2004, Roush et al. reported the only synthesis of landomycinone (**2**).[10] The key step of this approach was a moderately efficient Dötz benzannulation requiring a stoichiometric amount of organochromium reagent.

Herein, we wish to discuss our results on route to landomycinone (**2**) that led to the assembly of the skeleton of the target using transition-metal-catalyzed reactions as key steps.

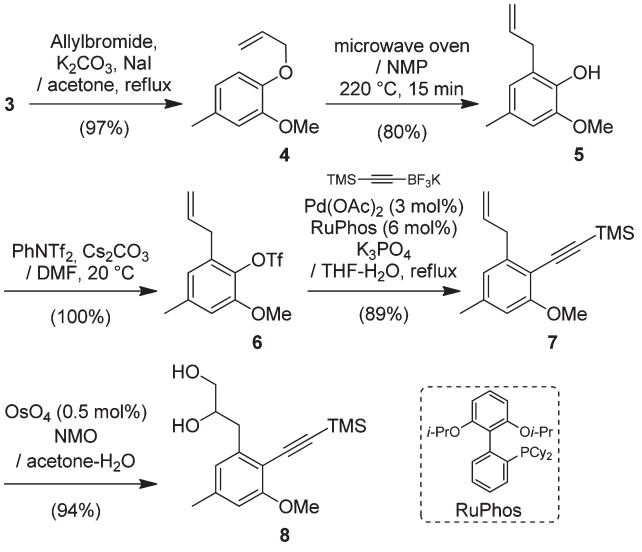
2. Results and Discussion

2.1. Retrosynthetic Plan. Due to its unique and densely hydroxylated polycyclic structure, landomycinone (**2**) is a difficult target. The most obvious challenge of its synthesis is the formation of the angular ring B which bears an asymmetric alcohol function particularly prone to elimination. We intended to design a strategy based on metal-catalyzed reactions (Scheme 1). The pivotal step, a [2 + 2 + 2] cycloaddition of alkynes, would allow the simultaneous construction of both rings B and C.[11,12] We planned other key

SCHEME 1. Retrosynthetic plan for the synthesis of 2



SCHEME 2. Functionalization of Ring A



transformations comprising a ring-closing metathesis (RCM) to create aromatic ring D[13] and a challenging Pd(0)-catalyzed cross-coupling at a sterically hindered *o*,*o*′-disubstituted position of ring A.

2.2. Preparation of the Diynes. Our synthesis started from allyl ether **4** obtained from the commercially available 2-methoxy-4-methylphenol **3** (Scheme 2).[14] Claisen rearrangement of allyl ether **4** was carried out in a microwave oven, using *N*-methylpyrrolidinone (NMP) as the solvent to improve microwave absorption.[15] The resulting phenol **5** was then converted into the corresponding triflate **6** in quantitative yield.

In the next stage, we focused our attention on the Pd(0)-catalyzed cross-coupling of **6** to introduce a (trimethylsilyl)ethynyl

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(9) Krohn, K.; Frese, P.; Freund, C. *Tetrahedron* **2000**, *56*, 1193–1196.
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(11) For reviews on [2 + 2 + 2] cycloadditions of alkynes, see: (a) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741–4767. (b) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307–2327. (c) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. *Org. React.* **2007**, *68*, 1–302. (d) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830–2834.
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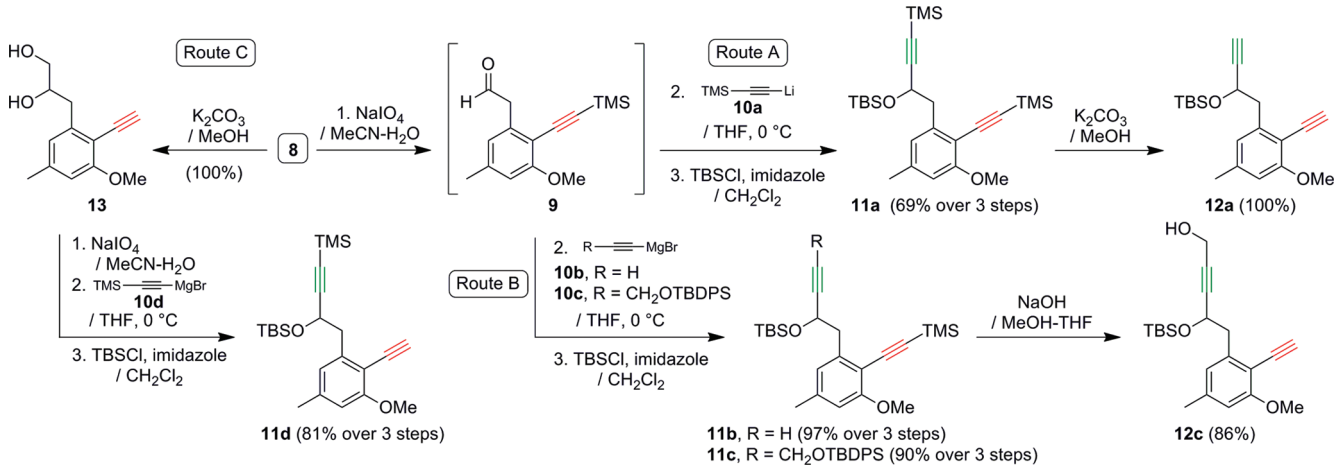
SCHEME 3. Preparation of Several Diynes for the [2 + 2 + 2] Cycloaddition

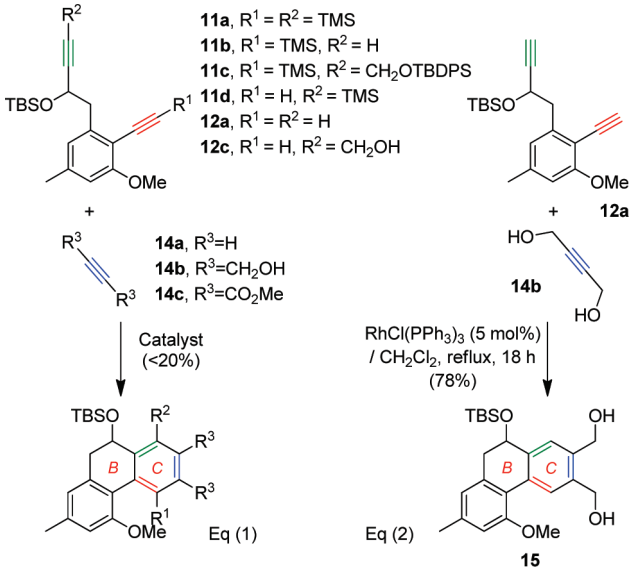


moiety. Unfortunately, classic Sonogashira conditions[16] did not lead to the desired product **7**, probably because of steric hindrance of the triflate function of **6**. These fruitless results prompted us to turn our attention toward a Suzuki−Miyaura cross-coupling involving potassium (trimethylsilyl)ethynyltrifluoroborate as the nucleophilic coupling partner.[17] To perform the cross-coupling efficiently and without loss of the trimethylsilyl group, an adaptation of the conditions described by Molander et al. was required.[17] Thus, the use of Buchwald's ligand RuPhos[18] along with a milder base (K_3PO_4 instead of Cs_2CO_3) led to the isolation of alkyne **7** in high yield. A selective osmium-catalyzed oxidation of the allyl group afforded then diol **8**, which served as precursor for the preparation of several diynes.

For this purpose, an oxidative cleavage was performed affording the fragile aldehyde **9** (Scheme 3, route A). Condensation with lithium (trimethylsilyl)acetylide **10a** furnished a propargylic alcohol, which was directly protected as the corresponding silyl ether **11a**. Afterward, diyne **12a** was easily obtained by removal of the acetylenic TMS protective groups under basic conditions. Alternatively, Grignard reagents **10b** and **10c** could be used in a similar sequence, enabling the synthesis of diynes **11b** and **11c** in good yields (Scheme 3, Route B). Subsequent treatment of compound **11c** with NaOH yielding alcohol **12c** by the selective cleavage of the *tert*-butyldiphenylsilyl (TBDPS) protective group orthogonally to the TBS.[19] Finally, a similar strategy yielded diyne **11d** from diol **13** (Scheme 3, route C).

2.3. Intermolecular [2 + 2 + 2] Cycloaddition. Many intermolecular [2 + 2 + 2] cycloadditions of substituted diynes

SCHEME 4. Attempts of Intermolecular [2 + 2 + 2] Cycloaddition



11a−d or **12c** were attempted using reaction partners such as acetylene (**14a**), but-2-yne-1,4-diol (**14b**) or dimethyl acetylenedicarboxylate (**14c**) (Scheme 4, eq 1). Several classic catalytic systems[11] ($RhCl(PPh_3)_3$,[20] $Rh(cod)_2BF_4$−H_8-BINAP,[21] Cp*Ru(cod)Cl,[22] $[Ir(cod)Cl]_2$-ddpe,[23] $Co_2(CO)_8$[24]) were screened but did not afford tricyclic compounds in synthetically useful yields (< 20%). The use of sterically hindered substituted diynes may account for these disappointing results. This hypothesis was confirmed by the successful Wilkinson's complex-catalyzed cycloaddition of the far less hindered bis-terminal diyne **12a** with but-2-yn-1,4-diol **14b**,

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(19) For other examples of such selective deprotections of TBDPS-ethers in the presence of TBS-ethers in natural product synthesis, see: (a) Kabat, M. M.; Lange, M.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 7701–7704. (b) Hatakeyama, S.; Irie, H.; Shintani, T.; Noguchi, Y.; Yamada, H.; Nishizawa, M. *Tetrahedron* **1994**, *50*, 13369–13376. (c) Cook, C.; Guinchard, X.; Liron, F.; Roulland, E. *Org. Lett.* **2010**, *12*, 744–747.
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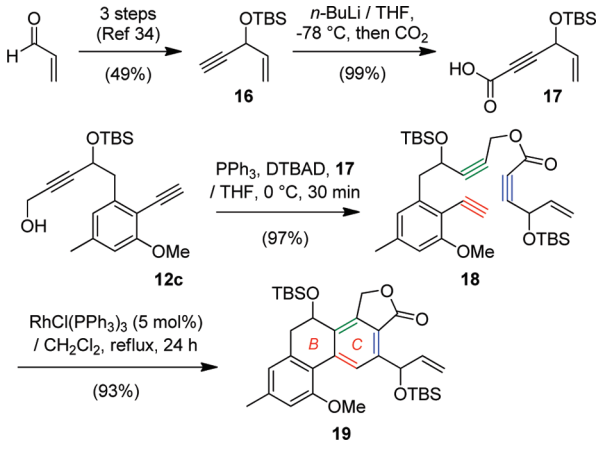
SCHEME 5. Construction of the Tether and Intramolecular [2 + 2 + 2] Cycloaddition



affording tricyclic product **15** in a 78% yield (Scheme 4, eq 2). Unfortunately, the C ring of product **15** does not bear the functionalities at positions C7 or C12 that would serve as precursor for the naphthoquinone motif of **2**.[25]

2.4. Intramolecular [2 + 2 + 2] Cycloaddition. The results presented above confirm that the [2 + 2 + 2] cycloaddition of substituted alkynes is difficult. Unfortunately, our strategy definitely required the cycloaddition of such substituted alkynes which is the only way to introduce oxidizable functions as precursors of the quinonic ring C. A popular solution of the problem is to render the [2 + 2 + 2] cycloaddition all-intermolecular by means of a cleavable tether. In such an approach, the negative effect of steric hindrance would be diminished by a more favorable entropy of the system. Moreover, regioselectivity would be ensured. Since the seminal examples by Nishiyama[26] and Stork,[27] the use of tethers,[28] in particular silicon-containing ones,[29] has become a classical synthetic method. In the case of [2+2+2] cyclodditions, a comparable strategy has already been applied with silicon-[30] and boron-containing[31] linkers. For our part, we chose to explore the interesting potential offered by the ester tether.[32] Esters, indeed, possess all required properties of an efficient tether: (i) many efficient methods are available for their installation, (ii) [2 + 2+2] cycloadditions of 1,6-diynes tied together by an ester bond are generally very efficient,[33] and (iii) the resulting lactone is a function with a rich reactivity.

To build our ester tether, carboxylic acid **17** was prepared in four steps from acrolein via known terminal alkyne **16** (Scheme 5).[34] The Mitsunobu reaction turned out to be the best method for the coupling of alcohol **12c** with carboxylic acid **17**.[35] Nonetheless, a thorough optimization of the conditions was necessary. The first trials were indeed very promising (isolated yield often reaching 80%) but poorly reproducible (yield sometimes dropped to 10−20%). Finally, we found that the order of addition of the various reagents was instrumental. Thus, the reproducibility issue was solved by premixing an excess of di-*tert*-butyl azodicarboxylate (DTBAD)[36] with PPh_3 in THF at 0 °C,[37] followed by the addition of 2 equiv of carboxylic acid with respect to the phosphine,[38] and then the addition of the alcohol. This procedure furnished ester **18** in a reproducible 97% yield.

With triyne **18** in hand, we searched for efficient [2 + 2 + 2] cycloaddition conditions. Delightfully, the reaction of **18** with the Wilkinson's catalyst (5 mol %, rt, 48 h) led to a full conversion furnishing tetracyclic product **19** in an 82% isolated yield, demonstrating the dramatic effect of the tether.[39] In refluxing CH_2Cl_2, the reaction time was shortened in half and the yield improved to 93%. One notices that the double bond present in the substrate **18** was inert to these conditions. Moreover, the latter conditions are sufficiently mild to avoid the troublesome aromatization of ring B by elimination of the oxygen at C6.[40]

2.5. Formation of Ring D by Ring-Closing Metathesis. Ring D was envisaged to arise by RCM followed by aromatization (Table 1). For this purpose, a second alkene function had to be introduced. Thus, selective addition[41] of vinyllithium to the lactone function of **19** led to the acid sensitive dienic hemiketal **20** as an inseparable mixture of four diastereoisomers.[42] Formation of aromatic compounds by RCM has been a very active research field over the past few years,[13] and it has been shown that newly formed rings bearing an alcohol or a ketone function could be readily aromatized by either elimination of water[43] or by tautomerization.[44] However, the corresponding transformation of a

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(31) Yamamoto, Y.; Ishii, J.-i.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712–3713.
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(39) Tethers built from diynoic acids and monalkyols were also prepared. They gave significantly worse results, [2 + 2 + 2] cycloaddition products being obtained in yield lower than 25%, along with many degradation products.
(40) For an example of a [2 + 2 + 2] cycloaddition accompanied by aromatization through elimination of TBDMSOH, see ref 12.
(41) Cavicchioli, S.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1984**, *49*, 1246–1251, and references therein
(42) (a) Compound **20** and all its derivatives are extremely acid-sensitive and tend to degrade via aromatization of ring B. More details concerning their handling are described in the Supporting Information. (b) These four diastereoisomers are a priori valuable, since the RCM-aromatization sequence should destroy two asymmetric centers.
(43) Selected examples: (a) Huang, K.-S.; Wang, E.-C. *Tetrahedron Lett.* **2001**, *42*, 6155–6157. (b) Yoshida, K.; Kawagoe, F.; Iwadate, N.; Takahashi, H.; Imamoto, T. *Chem. Asian J.* **2006**, *1*, 611–613. (c) Takahashi, H.; Yoshida, K.; Yanagisawa, A. *J. Org. Chem.* **2009**, *74*, 3632–3640.
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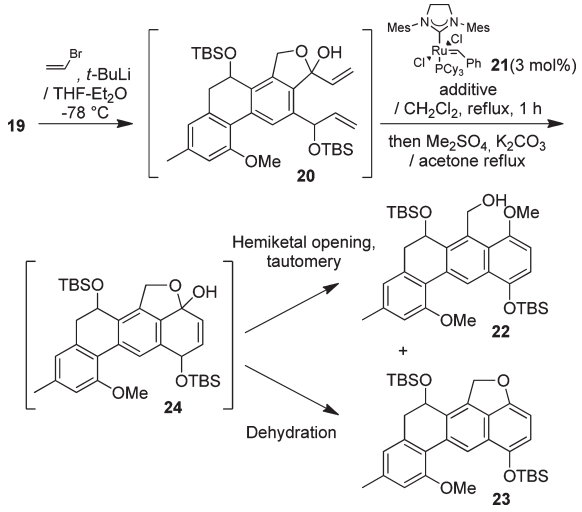
TABLE 1. Formation of Ring D by RCM



entry	additive	results[a]
1	no additive	**22** (33%) + **23** (28%)
2	2,6-dichlorobenzoquinone (10 mol %)[b]	only **23** (77%)
3	*B*-chlorocatecholborane (10 mol %)[b]	only **23**[c]
4	Ti(O*i*-Pr)$_4$ (1.5 equiv)[b]	no reaction
5	H_2O (1 equiv)[b]	**22** (19%) + **23** (27%)
6	$NaHCO_3$ (2 equiv)	degradation
7	Proton Sponge (20 mol %)[d]	degradation
8	**2,6-lutidine (20 mol %)**	**22 (54%) + 23 (13%)**
9	2,6-lutidine (1.1 equiv)[e]	**22** (43%) + **23** (25%)

[a]Isolated yields starting from lactone **19**. [b]5 mol % of catalyst **21** was used. [c]Product **23** was identified in the ^{1}H NMR of the reaction crude but not isolated. [d]1,8-Bis(dimethylamino)naphthalene. [e]2 h.

vinyl hemiketal, such as **20**, seems unprecedented. Reaction of diene **20** with Grubbs' second-generation catalyst **21**, followed by in situ protection of the unstable phenol as a methyl ether, afforded a mixture of cyclized compounds **22** and **23** in an almost 1:1 ratio (entry 1).

It is very likely that both **22** and **23** derive from common cyclized intermediate **24**, the aromatization occurring either by dehydration or by hemiketal opening followed by tautomerization (Table 1, scheme). The use of the Hoveyda−Grubbs second-generation catalyst did not improve these results. We then turned our attention toward the use of additives, which are common in RCM reactions. The addition of 2,6-dichlorobenzoquinone (entry 2)[45] or *B*-chlorocatecholborane (entry 3)[46] led to unwanted **23** exclusively, in up to 77% yield,[47] whereas the presence of Ti(O-*i*-Pr)$_4$ (entry 4) totally inhibited the RCM.[48] We thought that the addition of 1 equiv of water would disfavor the dehydration, but it had a negative impact on the outcome of the reaction (entry 5). We then realized that the desired phenol might acidify the reaction medium which enhances the formation of **23** by acid-catalyzed dehydration of intermediate **24**. Thus, buffering the reaction medium should diminish the formation of **23** in favor of **22**. Even though Grubbs' catalyst **21** is known to be sensitive to basic conditions,[49] we undertook a screening of weak non-nucleophilic bases. The addition of $NaHCO_3$ (entry 6) or Proton Sponge [1,8-bis(dimethylamino)-naphthalene] (entry 7) led to degradation products. We eventually found that 2,6-lutidine (20 mol %) (entry 8)[50] was mild enough to preserve the catalytic activity, while buffering the reaction medium efficiently, as we reproducibly isolated **22** in 54% yield and **23** in only 13%. Adding more 2,6-lutidine (entry 9) had no further positive impact. This last cyclization step allowed us to obtain the tetracyclic framework of landomycinone **2** with a remarkably high global yield of 19% over 15 steps.

Despite the success of the metathesis step described above, we chose to explore the possibility of forcing the opening of the five-membered lactol function of compound **20** prior to RCM (Scheme 6), in order to avoid the formation of compound **23**. We first tried to open the lactol ring by reduction, but the Luche conditions ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C)[51] or the use of $LiAlH_4$ (in THF or TBME, from room temperature to reflux) did not afford diol **25**, and extensive degradation of the starting material was the sole result. Degradation was also observed when we tried to form dicarbonyl **26** under oxidative conditions using IBX[52] or Dess−Martin periodinane[53] or under Oppenauer conditions [Al(O-*i*-Pr)$_3$, excess acetone, toluene, reflux].[54] Surprisingly, further attempts using MnO_2 or PCC[55] resulted only in the formation of lactone **19** by formal loss of the vinyl function. It has already been reported several times that the exposure of a lactol to silylating conditions might allow its opening by silylation of the masked alcohol.[56] Pleasingly, in the presence of TESCl and imidazole, lactol **20** rapidly and efficiently yielded α,β-unsaturated ketone **27**. This new diene **27** was, however, reluctant to RCM, even under forced conditions (Grubbs II or Hoveyda−Grubbs II catalysts, toluene, 80 °C, 12 h), as only a trace amount of naphthol **28** could be detected in the reaction mixture, along with some starting material and degradation products. Even the addition of Ti(O-*i*-Pr)$_4$, known to prevent deleterious catalyst complexation to carbonyl groups, was unsuccessful.[48]

2.6. Study of the Functionalization of Ring C. The next challenge was to cleave the benzylic alcohol function on ring C of compound **22**, which is a remnant of the tether, while installing an oxidizable function as a quinone precursor. We first envisioned removing this fragment using oxidative conditions that would provide an oxygen atom at position C7 (Scheme 7). For that purpose, the benzylic alcohol **22** was oxidized into the corresponding aldehyde **29** using a large

(45) This additive is usually employed to avoid double-bond migration in alkene metathesis: Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

(46) Vedrenne, E.; Dupont, H.; Oualef, S.; Elkaïm, L.; Grimaud, L. *Synlett* **2005**, 670–672.

(47) This efficient preparation of compound **23** prompted us to study its a posteriori opening, in order to convert it into a valuable intermediate. Nonetheless, its treatment with an oxidizing reagent, or with a nucleophile in the presence of a Lewis acid, were unsuccessful.

(48) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.

(49) Dinger, M. B.; Mol, J. C. *Eur. J. Inorg. Chem.* **2003**, 2827–2833.

(50) A single example of the use of 2,6-di(*tert*-butyl)pyridine as additive in an enyne metathesis had already been reported: Yoshida, K.; Shishikura, Y.; Takahashi, H.; Imamoto, T. *Org. Lett.* **2008**, *10*, 2777–2780.

(51) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

(52) Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812–2814.

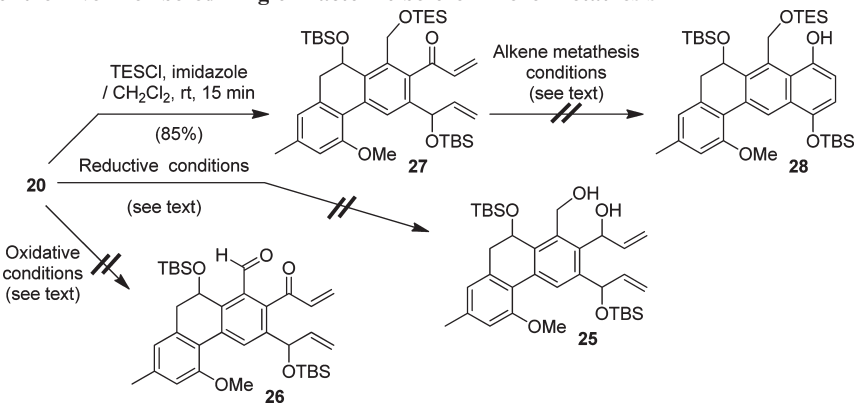
(53) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(54) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007–1017.

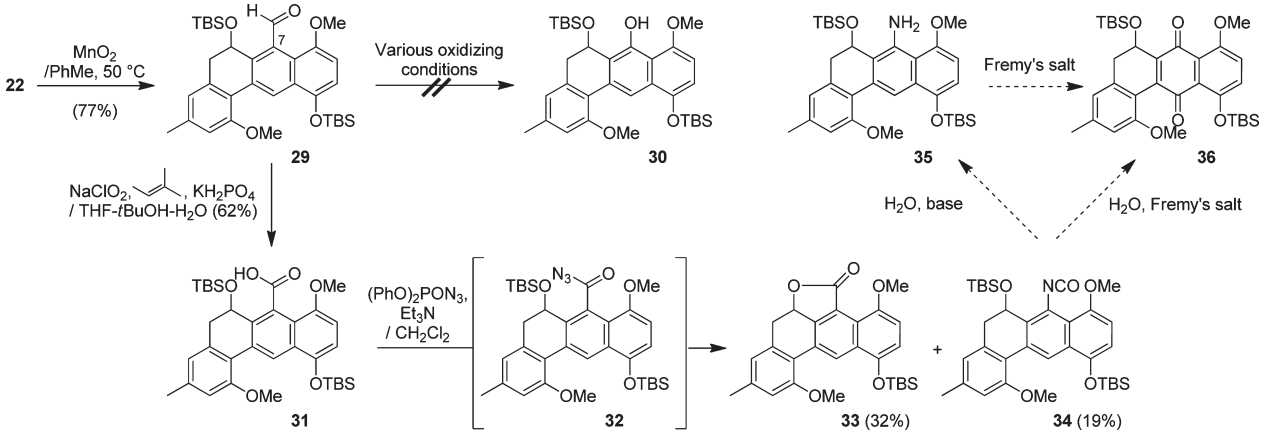
(55) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647–2650.

(56) For selected examples in natural product synthesis, see: (a) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403–4405. (b) White, J. D.; Wang, G.; Quaranta, L. *Org. Lett.* **2003**, *5*, 4983–4986.

SCHEME 6. Opening of the Five-Membered Ring of Lactol 20 before Alkene Metathesis



SCHEME 7. Removal of the Tether



excess of commercially available activated MnO_2.[57] Trials employing Dess−Martin,[53] Corey−Schmidt,[58] and Swern[59] conditions only afforded complex mixtures. Various Dakin oxidation conditions to transform aldehyde **29** into phenol **30** were tried (H_2O_2−K_2CO_3, H_2O_2−PhSeSePh,[60] *m*-CPBA,[61] AcOOH, Oxone[62]), but none of them afforded the expected product.

Searching for an alternative cleavage of this C−C bond, we turned our attention toward Curtius rearrangement.[63] To test this option, aldehyde **29** was oxidized using Lindgren−Kraus−Pinnick reaction conditions,[64] giving the corresponding carboxylic acid **31** in 62% yield. We then used $(PhO)_2PON_3$ to transform **31** into the acyl azide **32**.[65] However, in the presence of triethylamine, either in DMF or in dichloromethane, this reagent afforded complex mixtures that did not contain acyl azide **32** but led in low yield to the pentacyclic γ-lactone **33**, along with isocyanate **34**, the desired Curtius rearrangement product. The instability of the intermediate **32** is unusual; its room-temperature rearrangement is likely initiated by the release of steric constraints through expulsion of a molecule of N_2. The unexpected formation of γ-lactone **33** might be due to trapping of the neighboring acylium cation resulting from the loss of N_3^- from acyl azide **32** by the OTBS group at C6 or from the direct $(PhO)_2PON_3$ activation of the carboxylic acid function of **31**. Despite the low observed yields for this last step, we have validated our strategy, as we successfully removed the tether used for the rhodium-catalyzed [2 + 2 + 2] cycloaddition while installing a nitrogen atom as a precursor of the quinonic ring C. By modifying the nature of the protective group at C6, we should obtain better yields for this step. We envision finishing the total synthesis of landomycinone (**2**) by performing the hydrolysis of isocyanate **34** affording then aniline **35** that would deliver the targeted quinone **36** by oxidation by Fremy's salt (Scheme 7).[66] At the end game, the methyl protecting groups on the phenol functions would be removed employing Lewis acids such as BCl_3[67] or MgI_2[68] in the mild conditions usually used for

(57) Purchased from Sigma-Aldrich and used shortly after opening the container. "Older" MnO_2 proved not reactive enough, whereas highly activated MnO_2 produced from $KMnO_4$ and $MnCl_2 \cdot 4H_2O$ (Fatiadi, A. J. *Synthesis* **1978**, 65–104) yielded a complex mixture

(58) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399–402.

(59) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.

(60) Syper, L. *Synthesis* **1989**, 167–172.

(61) Franck, R. W.; Gupta, R. B. *J. Org. Chem.* **1985**, *50*, 4632–4635.

(62) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031–1034.

(63) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.

(64) (a) Lindgren, B. O.; Nilson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890. (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175–1176. (c) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.

(65) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.

(66) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229–246.

(67) Nagaoka, H.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899–902.

(68) Yamaguchi, S.; Nedachi, M.; Yokoyama, H.; Hirai, Y. *Tetrahedron Lett.* **1999**, *40*, 7363–7365.

OMe neighboring carbonyl functions, and the TBS would be removed under acidic conditions as already described by Roush.[10a]

3. Conclusion

The densely functionalized and highly unsaturated tetracyclic skeleton of landomycinone (**2**) has been efficiently synthesized using three metal-catalyzed pivotal steps. First, finely tuned conditions were designed to perform an efficient Suzuki−Miyaura cross-coupling between potassium (trimethylsilyl)ethynyltrifluoroborate and the sterically hindered aromatic triflate **6**. Second, a remarkably efficient Rh(I)-catalyzed [2 + 2 + 2] cycloaddition allowed the concomitant formation of rings B and C, delivering lactone **19**. This key intermediate has been synthesized in twelve steps and in a 50% overall yield. Third, a RCM under specially designed buffered conditions has secured the formation of aromatic ring D. Finally we have validated our strategy, as the tether used for the Rh(I)-catalyzed [2 + 2 + 2] cycloaddition was replaced by an oxidizable function that prefigures quinonic ring C. Further improvements and developments based on this promising strategy are currently under investigation and will be reported in due course.

4. Experimental Section

2-Allyl-6-methoxy-4-methylphenol (5). A solution of allyl ether **4** (5.94 g, 33.3 mmol, 1 equiv) in NMP (12 mL) was irradiated in a microwave oven (T = 220 °C, t = 15 min). The reaction mixture was then diluted with water (75 mL) and extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with water (75 mL) and brine (75 mL), dried over Na_2SO_4, and filtered, and the solvents were removed under reduced pressure. Purification by flash chromatography (heptane/EtOAc, 20:1−14:1) afforded phenol **5** (4.87 g, 27.3 mmol, 80%) as a pale yellow oil. The spectroscopic and analytical data were in accordance with those reported in the literature:[14] R_f 0.14 (heptane/toluene, 1:1); IR (neat) ν (cm^{-1}) 3528, 3076, 3003, 2915, 2842, 1606, 1495, 1425, 1362, 1291, 1232, 1148, 1073, 907, 831; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm) 6.561 (s, 1H), 6.555 (s, 1H), 6.00 (ddt, J = 16.8, 10.1, and 6.4 Hz, 1H), 5.50 (s, 1H), 5.11−5.01 (m, 2H), 3.86 (s, 3H), 3.37 (d, J = 6.4 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C (ppm) 146.3 (Cq), 141.2 (Cq), 137.0 (CH), 128.9 (Cq), 125.6 (Cq), 122.6 (CH), 115.5 (CH_2), 109.8 (CH), 56.1 (CH_3), 34.0 (CH_2), 21.2 (CH_3); LRMS (ESI) m/z 201 [M + Na]$^+$; HRMS (ESI) m/z calcd for $C_{11}H_{14}O_2$ [M + Na]$^+$ 201.0891, found 201.0877.

[(2-Allyl-6-methoxy-4-methylphenyl)ethynyl]trimethylsilane (7). $Pd(OAc)_2$ (12.9 mg, 57.5 μmol, 3 mol %), RuPhos (53.7 mg, 0.115 mmol, 6 mol %), potassium (trimethylsilyl)ethynyltrifluoroborate (587 mg, 2.88 mmol, 1.5 equiv), and K_3PO_4 (1.63 g, 7.67 mmol, 4 equiv) were placed in a 25-mL flask equipped with a condenser. A solution of triflate **6** (595 mg, 1.92 mmol, 1 equiv) in THF (5.7 mL) and degassed water (570 μL) were added, and the reaction mixture was refluxed for 4 h. Filtration on a short pad of silica gel (elution with Et_2O) followed by purification by flash chromatography (heptane/toluene, 8:2−6:4) afforded alkyne **7** (440 mg, 1.70 mmol, 89%) as a yellow oil: R_f 0.35 (heptane/EtOAc, 10:1); IR (neat) ν (cm^{-1}) 2958, 2837, 2150, 1607, 1568, 1462, 1318, 1249, 1154, 1078, 860, 840, 759; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm) 6.63 (s, 1H), 6.53 (s, 1H), 5.97 (ddd, J = 17.1, 10.1, and 6.7 Hz, 1H), 5.10 (dd, J = 17.1 and 1.2 Hz, 1H), 5.04 (dd, J = 10.1 and 1.2 Hz, 1H), 3.85 (s, 3H), 3.50 (d, J = 6.7 Hz, 2H), 2.31 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C (ppm) 160.7 (Cq), 144.6 (Cq), 139.9 (Cq), 136.7 (CH), 122.0 (CH), 115.9 (CH_2), 109.4 (CH), 109.1 (Cq), 102.4 (Cq), 100.1 (Cq), 56.0 (CH_3), 39.0 (CH_2), 22.1 (CH_3), 0.3 (3 × CH_3); LRMS (ESI) m/z 281 [M + Na]$^+$, 313 [M + MeOH + Na]$^+$; HRMS (ESI) m/z calcd for $C_{16}H_{22}OSi$ [M + Na]$^+$ 281.1338, found 281.1350.

[10-(*tert*-Butyldimethylsilyloxy)-5-methoxy-7-methyl-9,10-dihydrophenanthrene-2,3-diyl]dimethanol (15). A solution of diyne **12a** (54.9 mg, 0.167 mmol, 1 equiv) in degassed EtOH (3 mL) was added to $RhCl(PPh_3)_3$ (7.7 mg, 8.4 μmol, 5 mol %) and but-2-yne-1,4-diol **14b** (71.9 mg, 0.836 mmol, 5 equiv). The reaction mixture was refluxed for 16 h, diluted with water (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with water (10 mL), dried over Na_2SO_4, and filtered, and the solvents were removed under reduced pressure. Purification by flash chromatography (heptane/EtOAc, 1:1) afforded tricyclic diol **15** (54.0 mg, 0.130 mmol, 78%) as a colorless amorphous solid: R_f 0.20 (heptane/EtOAc, 1:1); IR (neat) ν (cm^{-1}) 3330, 2928, 2855, 1611, 1580, 1461, 1318, 1255, 1170, 1093, 1056, 1006, 934, 904, 868, 835, 776; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm) 8.25 (s, 1H), 7.54 (s, 1H), 6.73 (s, 1H), 6.71 (s, 1H), 4.85−4.73 (m, 5H), 3.89 (s, 3H), 2.92−2.77 (m, 4H), 2.36 (s, 3H), 0.99 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C (ppm) 156.9 (Cq), 141.5 (Cq), 138.7 (Cq), 137.84 (Cq), 137.75 (Cq), 137.2 (Cq), 132.1 (Cq), 129.8 (CH), 125.3 (CH), 122.2 (CH), 119.7 (Cq), 111.6 (CH), 69.6 (CH), 64.9 (CH_2), 64.8 (CH_2), 55.7 (CH_3), 40.0 (CH_2), 26.1 (3 × CH_3), 21.7 (CH_3), 18.5 (Cq), −4.3 (CH_3), −4.7 (CH_3); LRMS (ESI) m/z 437 [M + Na]$^+$, 851 [2M + Na]$^+$; HRMS (ESI) m/z calcd for $C_{24}H_{34}O_4Si$ [M + Na]$^+$ 437.2124, found 437.2115.

4-(*tert*-Butyldimethylsilyloxy)-5-(2-ethynyl-3-methoxy-5-methylphenyl)pent-2-ynyl 4-(*tert*-butyldimethylsilyloxy)hex-5-en-2-ynoate (18). Di-*tert*-butyl diazodicarboxylate (463 mg, 2.01 mmol, 1.8 equiv) and PPh_3 (468 mg, 1.79 mmol, 1.6 equiv) were placed in a 50-mL flask at 0°C. THF (3 mL) was added, affording a yellow solution that was allowed to reach room temperature and stirred for 30 min, resulting in an off-white suspension. The reaction medium was cooled to 0°C before dropwise addition of a solution of carboxylic acid **17** (858 mg, 3.57 mmol, 3.2 equiv) in THF (4 mL);the reaction mixture became clear again. Then, 15 min later, a solution of alcohol **12c** (400 mg, 1.12 mmol, 1 equiv) in THF (4 mL) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min. This mixture was then diluted with an saturated aqueous solution of $NaHCO_3$ (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with water (25 mL) and brine (25 mL), dried over Na_2SO_4, and filtered, and the solvents were removed under reduced pressure. Filtration through a short pad of silica gel (elution with heptane/EtOAc, 4:1) followed by purification by flash chromatography (heptane/EtOAc, 30:1 to 25:1) afforded pure ester **18** (629 mg, 1.08 mmol, 97%) as a colorless amorphous solid: R_f 0.43 (heptane/EtOAc, 4:1); IR (neat) ν (cm^{-1}) 3310, 2954, 2929, 2856, 2237, 2102, 1723, 1608, 1570, 1462, 1362, 1315, 1229, 1144, 1087, 941, 836, 778; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm) 6.71 (s, 1H,), 6.59 (s, 1H), 5.89 (ddd, J = 16.8, 10.1, and 4.9 Hz, 1H), 5.44 (d, J_{trans} = 16.8 Hz, 1H), 5.23 (d, J_{cis} = 10.1 Hz, 1H), 5.00 (d, J = 4.9 Hz, 1H), 4.77 (s, 2H), 4.68 (dd, J = 8.2 and 5.8 Hz, 1H), 3.88 (s, 3H), 3.49 (s, 1H), 3.14 (dd, J = 12.8 and 5.8 Hz, 1H), 3.07 (dd, J = 12.8 and 8.2 Hz, 1H), 2.33 (s, 3H), 0.92 (s, 9H), 0.82 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H), −0.02 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C (ppm) 161.0 (Cq), 152.7 (Cq), 141.5 (Cq), 139.8 (Cq), 135.8 (CH), 124.9 (CH), 116.6 (CH_2), 109.9 (CH), 108.2 (Cq), 89.2 (Cq), 87.5 (Cq), 85.0 (CH), 78.7 (Cq), 77.5 (Cq), 76.3 (Cq), 63.6 (CH), 62.8 (CH), 56.1 (CH_3), 53.8 (CH_2), 43.5 (CH_2), 25.84 (3 CH_3), 25.80 (3 × CH_3), 22.0 (CH_3), 18.4 (Cq), 18.3 (Cq), −4.5 (CH_3), −4.8 (CH_3), 4.9 (CH_3), −5.2 (CH_3); LRMS (ESI) m/z 603 [M + Na]$^+$; HRMS (ESI) m/z calcd for $C_{33}H_{48}O_5Si_2$ [M + Na]$^+$ 603.2947, found 603.2938.

4-(*tert*-Butyldimethylsilyloxy)-11-(1-(*tert*-butyldimethylsilyloxy)allyl)-9-methoxy-7-methyl-4,5-dihydrophenanthro[1,2-*c*]-furan-1(3*H*)-one (19). A solution of $RhCl(PPh_3)_3$ (30.7 mg, 33.1 μmol, 5 mol %) in CH_2Cl_2 (2 mL) was added to a solution of triyne **18** (385 mg, 0.663 mmol, 1 equiv) in CH_2Cl_2 (5 mL). The reaction mixture was refluxed for 24 h and then filtered through a short pad of silica gel (elution with heptane/EtOAc, 10:1). Purification by flash chromatography (heptane/EtOAc, 30:1−25:1) afforded a mixture of both diastereoisomers of the tetracyclic lactone **19** (360 mg, 0.620 mmol, 93%) as a white solid. The two diastereoisomers were separated by preparative HPLC (Ø 16 mm; 12 mL·min^{-1}; heptane/EtOAc, 30:1) affording two samples from a 20 mg aliquot. Diastereoisomer A (9.0 mg) was obtained as a white solid and diastereoisomer B (11.4 mg) as a colorless amorphous solid. Their absolute configuration was not determined. Diastereoisomer A: R_f 0.65 (heptane/EtOAc, 10:1, 2 elutions); IR (neat) ν (cm^{-1}) 2953, 2928, 2855, 1751, 1606, 1593, 1462, 1348, 1316, 1253, 1210, 1095, 1053, 1027, 1004, 912, 853, 834, 777, 681; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm) 8.57 (s, 1H), 6.75 (s, 1H), 6.69 (s, 1H), 6.49 (d, J = 5.2 Hz, 1H), 5.93 (ddd, J = 17.1, 10.4, and 5.2 Hz, 1H), 5.66 (d, J = 15.9 Hz, 1H), 5.40 (d, J_{trans} = 17.1 Hz, 1H), 5.37 (d, J = 15.9 Hz, 1H), 4.98 (m, 2H), 3.89 (s, 3H), 2.89 (dd, J = 14.0 and 11.9 Hz, 1H), 2.82 (dd, J = 14.0 and 4.6 Hz, 1H), 2.37 (s, 3H), 0.97 (s, 18H), 0.20 (s, 3H), 0.17 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C (ppm) 171.0 (Cq), 157.4 (Cq), 143.6 (Cq), 142.2 (Cq), 141.2 (CH), 140.2 (Cq), 138.0 (Cq), 137.3 (Cq), 133.7 (Cq), 127.0 (CH), 121.8 (CH), 119.6 (Cq), 119.2 (Cq), 113.3 (CH_2), 111.9 (CH), 70.9 (CH_2), 70.8 (CH), 69.0 (CH), 55.8 (CH_3), 40.2 (CH_2), 26.2 (3 × CH_3), 26.1 (3 × CH_3), 21.8 (CH_3), 18.6 (Cq), 18.3 (Cq), −3.7 (CH_3), −4.4 (CH_3), −4.5 (CH_3), −4.7 (CH_3); LRMS (ESI) m/z 603 [M + Na]$^+$; HRMS (ESI) m/z calcd for $C_{33}H_{48}O_5Si_2$ [M + Na]$^+$ 603.2938, found 603.2935. Diastereoisomer B: R_f 0.58 (heptane/EtOAc, 10:1, 2 elutions); IR (neat) ν (cm^{-1}) 2953, 2928, 2856, 1753, 1606, 1594, 1461, 1348, 1317, 1253, 1211, 1096, 1055, 1029, 1004, 913, 855, 835, 777, 680; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm) 8.67 (s, 1H), 6.76 (s, 1H), 6.71 (s, 1H), 6.37 (d, J = 5.2 Hz, 1H), 6.06 (ddd, J = 17.1, 10.4, and 5.2 Hz, 1H), 5.65 (d, J = 15.6 Hz, 1H), 5.47 (d, J_{trans} = 17.1 Hz, 1H), 5.38 (d, J = 15.6 Hz, 1H), 5.04 (d, J_{cis} = 10.4 Hz, 1H), 4.96 (dd, J = 11.9 and 4.6 Hz, 1H), 3.89 (s, 3H), 2.95 (dd, J = 14.3 and 11.9 Hz, 1H), 2.85 (dd, J = 14.3 and 4.6 Hz, 1H), 2.38 (s, 3H), 0.96 (s, 9H), 0.92 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C (ppm) 171.0 (Cq), 157.4 (Cq), 143.5 (Cq), 142.3 (Cq), 141.2 (CH), 140.2 (Cq), 138.0 (Cq), 137.3 (Cq), 133.4 (Cq), 126.9 (CH), 122.0 (CH), 119.7 (Cq), 119.2 (Cq), 113.2 (CH_2), 111.9 (CH), 70.9 (CH_2), 70.5 (CH), 69.1 (CH), 55.7 (CH_3), 40.1 (CH_2), 26.2 (3 CH_3), 26.0 (3 CH_3), 21.8 (CH_3), 18.4 (Cq), 18.3 (Cq), −3.8 (CH_3), −4.4 (CH_3), −4.6 (CH_3), −4.7 (CH_3); LRMS (ESI) m/z 603 [M + Na]$^+$; HRMS (ESI) m/z calcd for $C_{33}H_{48}O_5Si_2$ [M + Na]$^+$ 603.2938, found 603.2927.

[6,11-Bis(*tert*-butyldimethylsilyloxy)-1,8-dimethoxy-3-methyl-5,6-dihydrotetraphen-7-yl]methanol (22). 2,6-Lutidine (103 μL of a freshly prepared 1.0 M solution in CH_2Cl_2, 0.103 mmol, 20 mol %) was added to a solution of diene **20** (314 mg, 0.516 mmol, 1 equiv) in CH_2Cl_2 (10 mL). A solution of Grubbs II catalyst (13.2 mg, 15.5 μmol, 3 mol %) in CH_2Cl_2 (5 mL) was added, and the reaction mixture was refluxed for 1 h. K_2CO_3 (357 mg, 2.58 mmol, 5 equiv), acetone (10 mL), and Me_2SO_4 (98 μL, 1.03 mmol, 2 equiv) were successively added, and the reflux was maintained during 10 h. Filtration through a short pad of neutralized silica gel (elution with heptane/EtOAc, 4:1) followed by purification by flash chromatography (neutralized silica gel; heptane/EtOAc, 50:1−4:1) afforded benzylic alcohol **22** (167 mg, 0.281 mmol, 54%) as a light brown solid. Cyclic ether **23** (37.8 mg, 67.2 μmol, 13%) was also isolated as a byproduct: R_f 0.30 (heptane/EtOAc, 4:1); IR (neat) ν (cm^{-1}) 3500, 2928, 2855, 1612, 1575, 1461, 1360, 1304, 1251, 1171, 1113, 1003, 970, 934, 834, 776; ^{1}H NMR (500 MHz, C_6D_6) δ_H (ppm) 9.63 (s, 1H), 6.79 (d, J = 8.5 Hz, 1H), 6.66 (s, 1H), 6.59 (s, 1H), 6.36 (d, J = 8.5 Hz, 1H), 5.96 (dd, J = 3.1 and 2.4 Hz, 1H), 5.53 (dd, J = 12.1 and 4.6 Hz, 1H), 5.44 (dd, J = 12.1 and 11.0 Hz, 1H), 3.51 (s, 3H), 3.33 (dd, J = 11.0 and 4.6 Hz, 1H), 3.26 (s, 3H), 3.03 (dd, J = 15.6 and 3.1 Hz, 1H), 2.87 (dd, J = 15.6 and 2.4 Hz, 1H), 2.23 (s, 3H), 1.15 (s, 9H), 0.80 (s, 9H), 0.32 (s, 3H), 0.20 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75.5 MHz, C_6D_6) δ_C (ppm) 157.7 (Cq), 151.0 (Cq), 147.0 (Cq), 138.0 (Cq), 137.1 (Cq), 135.8 (Cq), 130.5 (Cq), 129.9 (Cq), 125.1 (Cq),124.0 (CH), 123.4 (CH), 121.4 (Cq), 117.1 (Cq), 112.0 (CH), 111.8 (CH), 106.0 (CH), 65.1 (CH), 60.3 (CH_2), 55.7 (CH_3), 55.5 (CH_3), 39.3 (CH_2), 26.2 (3 × CH_3), 26.0 (3 × CH_3), 21.5 (CH_3), 18.7 (Cq), 18.3 (Cq), −3.5 (CH_3), −3.8 (CH_3), −4.2 (CH_3), −4.3 (CH_3); LRMS (ESI) m/z 445 [M − TBSOH − H_2O + H]$^+$, 617 [M + Na]$^+$, 649 [M+MeOH + Na]$^+$; HRMS (ESI) m/z calcd for $C_{34}H_{50}O_5Si_2$ [M + Na]$^+$ 617.3095, found 617.3104; mp 155−156 °C (EtOAc/heptane).

[7-Methoxy-9-methyl-11,12-dihydro-1*H*-tetrapheno[8,7-*bc*]-furan-5,12-diyl)bis(oxy)]bis(*tert*-butyldimethylsilane) (23). 2,6-Dichlorobenzoquinone (2.4 mg, 13.4 μmol, 10 mol %) was added to a solution of diene **20** (81.5 mg, 0.134 mmol, 1 equiv) in CH_2Cl_2 (3.5 mL). A solution of Grubbs II catalyst (5.7 mg, 6.7 μmol, 5 mol %) in CH_2Cl_2 (3 mL) was added, and the reaction mixture was refluxed for 1 h. Filtration through a short pad of neutralized silica gel (elution with heptane/EtOAc, 10:1) followed by purification by flash chromatography (neutralized silica gel; heptane/EtOAc, 50:1) afforded cyclic ether **23** (57.7 mg, 0.103 mmol, 77%) as a pale yellow foam: R_f 0.57 (heptane/EtOAc, 4:1); IR (neat) ν (cm^{-1}) 2953, 2929, 2856, 1610, 1574, 1474, 1428, 1371, 1316, 1255, 1102, 1042, 1007, 979, 912, 856, 837, 777, 702; ^{1}H NMR (500 MHz, C_6D_6) δ_H (ppm) 9.28 (s, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.72 (s, 1H), 6.69 (s, 1H), 6.26 (d, J = 15.0 Hz, 1H), 5.96 (d, J = 15.0 Hz, 1H), 4.98 (dd, J = 11.6 and 4.0 Hz, 1H), 3.67 (s, 3H), 3.53 (dd, J = 13.7 and 11.6 Hz, 1H), 2.93 (dd, J = 13.7 and 4.0 Hz, 1H), 2.30 (s, 3H), 1.30 (s, 9H), 1.01 (s, 9H), 0.41 (s, 3H), 0.34 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75.5 MHz, C_6D_6) δ_C (ppm) 157.6 (Cq), 156.9 (Cq), 143.7 (Cq), 138.3 (Cq), 137.4 (Cq), 133.7 (Cq), 132.7 (Cq), 131.5 (Cq), 130.0 (Cq), 125.9 (Cq), 122.3 (CH), 122.0 (Cq), 121.0 (CH), 116.1 (CH), 112.2 (CH), 100.0 (CH), 79.0 (CH_2), 71.3 (CH), 55.4 (CH_3), 41.2 (CH_2), 26.24 (3 × CH_3), 26.19 (3 × CH_3), 21.5 (CH_3), 18.7 (Cq), 18.3 (Cq), −4.0 (CH_3), −4.1 (CH_3), −4.3 (CH_3), −4.7 (CH_3); LRMS (ESI) m/z 585 [M + Na]$^+$; HRMS (ESI) m/z calcd for $C_{33}H_{46}O_4Si_2$ [M + Na]$^+$ 585.2832, found 585.2847.

6,11-Bis(*tert*-butyldimethylsilyloxy)-7-isocyanato-1,8-dimethoxy-3-methyl-5,6-dihydrotetraphene (34). Et_3N (15 μL, 0.104 mmol, 3 equiv) and $(PhO)_2PON_3$ (16 μL, 69.2 μmol, 2 equiv) were successively added to a solution of carboxylic acid **31** (24.8 mg, 34.6 μmol, 1 equiv) in CH_2Cl_2 (700 μL), and the reaction mixture was stirred at room temperature for 1 h. Filtration on neutralized silica (elution with CH_2Cl_2) and evaporation of the solvent at room temperature, followed by purification by flash chromatography (neutralized silica; Pent/Et_2O, 20:1−10:1) afforded isocyanate **34** (4.0 mg, 6.6 μmol, 19%) as a colorless amorphous solid. Lactone **33** was also isolated from the reaction mixture: R_f 0.54 (heptane/EtOAc, 4:1); IR (neat) ν (cm^{-1}) 2928, 2855, 2284 (N=C=O), 1611, 1593, 1461, 1333, 1316, 1288, 1259, 1104, 1070, 970, 933, 901, 835, 777; ^{1}H NMR (500 MHz, C_6D_6) δ_H (ppm) 9.46 (s, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.70 (s, 1H), 6.55 (s, 1H), 6.29 (d, J = 8.2 Hz, 1H), 5.67 (dd, J = 2.7 and 2.1 Hz, 1H), 3.54 (s, 3H), 3.49 (s, 3H), 2.96 (dd, J = 15.3 and 2.7 Hz, 1H), 2.74 (dd, J = 15.3 and 2.1 Hz, 1H), 2.20 (s, 3H), 1.13 (s, 9H), 0.79 (s, 9H), 0.29 (s, 3H), 0.19 (s, 3H), 0.18 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125.8 MHz, C_6D_6) δ_C (ppm) 157.7 (Cq), 150.8 (Cq),

146.1 (Cq), 138.5 (Cq), 137.3 (Cq), 132.8 (Cq), 130.8 (Cq), 130.4 (Cq), 125.8 (Cq), 125.2 (Cq), 123.3 (CH), 121.6 (CH), 120.2 (Cq), 113.0 (CH), 111.6 (CH), 105.4 (CH), 64.6 (CH), 55.5 (CH_3), 55.1 (CH_3), 39.3 (CH_2), 26.1 (3 × CH_3), 25.9 (3 × CH_3), 21.6 (CH_3), 18.6 (Cq), 18.4 (Cq), −3.9 (CH_3), −4.2 (2 * CH_3), −4.5 (CH_3); one carbon signal was not visualized (probably hidden by the solvent signal); LRMS (ESI) *m*/*z* 628 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{34}H_{47}NO_5Si_2$ $[M + Na]^+$ 628.2891, found 628.2895.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.