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Synthesis of Phosphonomethyl Tetrahydrofurans via the Mori–Tamaru Reaction of Phosphonodienes

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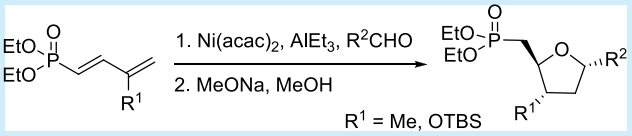
ABSTRACT: Nickel-catalyzed reductive addition of phosphonodienes to aldehydes (the Mori–Tamaru reaction) gives hydroxy vinyl phosphonates in good yields with excellent control of the relative stereochemistry. Base-induced cyclization of the vinyl phosphonates yields phosphonomethyl-substituted tetrahydrofurans. Inversion of the hydroxyl stereochemistry by Mitsunobu reaction and then cyclization yields a different set of phosphonomethyl-substituted tetrahydrofuran diastereoisomers.



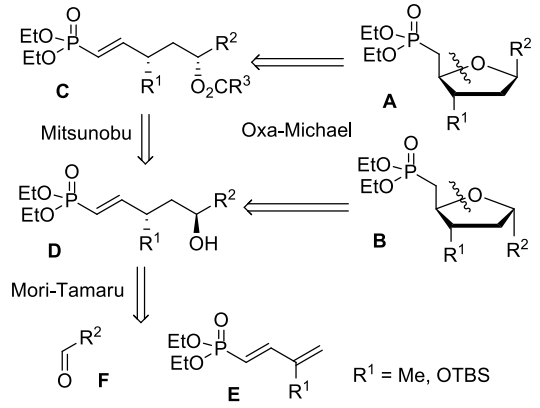
C-Nucleosides are hydrolytically stable analogues of N-nucleosides, examples of which appear in nature.[1] This modification of the basic nucleoside structure leads to several compounds that show interesting antiviral and anticancer activity.[1,2] For example, the C-nucleotide remdesivir (GS-5734)[3] has recently seen renewed interest because of its activity against single-stranded RNA viruses, including various corona viruses.[4] Furthermore, in several synthetic C-nucleoside analogues, the typical nucleoside nitrogen heterocycle can be replaced other heterocycles or substituted benzene rings with retention of the biological activity.[2]

Similarly, phosphonates are often prepared as more metabolically stable analogues of biological phosphates.[5] Several non-isosteric phosphonate analogues of nucleoside phosphates have been synthesized,[6] although in general they possess limited biological activity. Furthermore, this approach has been applied for analogues of ribose-1-phosphate and other important anomeric phosphates.[7]

We saw the need for a synthetic approach that could address the installation of both the C-nucleoside and the phosphonate while also introducing the correct relative stereochemistry of the substituents. A retrosynthetic analysis (Scheme 1) revealed that the heterocyclic ring (**A** or **B**) could be formed via an oxa-Michael reaction, wherein a hydroxyl nucleophile adds across a vinyl phosphonate (**C** or **D**). On the basis of recent experience,[8] it was recognized that the 1,3-subsitution pattern next to an alkene (**D**) could result from the Mori–Tamaru reaction[9,10] between a diene (**E**) and an aldehyde (**F**). However, the stereochemistry of the carbinol carbon would need to be corrected by a Mitsunobu reaction (**D** to **C**) in order to give a tetrahydrofuran with the appropriate disposition of the substituents found in C-nucleosides. Once the relative stereochemistry is set in the Mori–Tamaru and Mitsunobu reactions, the cyclization is expected to follow the precedent established with related unsaturated esters.[11]

In the Mori–Tamaru reaction,[9,10] a variety of 1- and 2-substituted 1,3-dienes in combination with catalytic $Ni(acac)_2$ and either Et_3B or Et_2Zn react (homoallylation) with aldehydes to give bis-homoallylic alcohols with very high 1,3-*anti* or 1,2-*anti* diastereoselectivity. We applied this reaction to the construction of the tetrahydrofuran-containing C1–C9 fragment **1** of amphidinolides C and F.[8] The key steps in this synthesis (Scheme 2) were the Mori–Tamaru reaction to set the stereochemistry (**2**), cross-metathesis (**3**), and base-induced cyclization to form the tetrahydrofuran **4**. We subsequently showed that the metathesis step can be avoided by using ester-functionalized diene **5** in the Mori–Tamaru reaction.[12]

Scheme 1. Retrosynthetic Analysis for Phosphonomethyl Tetrahydrofurans



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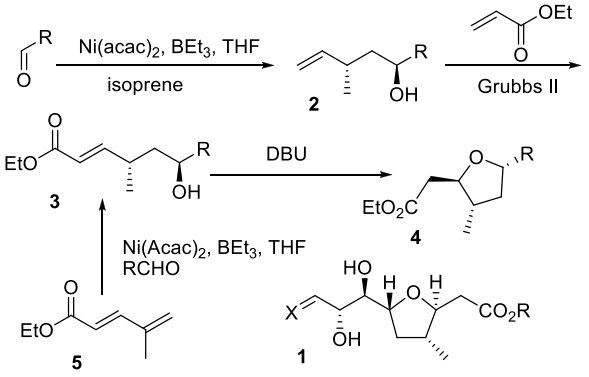
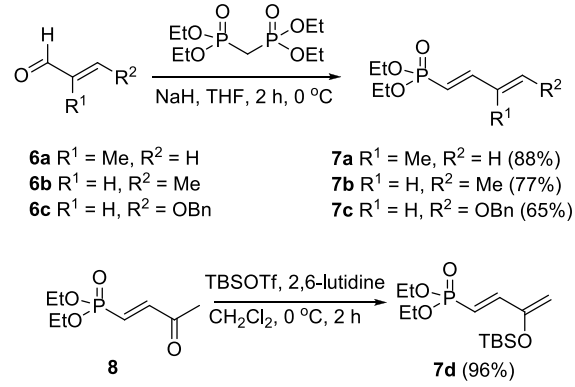
Scheme 2. Application of the Mori–Tamaru Reaction to Tetrahydrofuran Synthesis



The Mori–Tamaru reaction of phosphonodienes is unexplored, and the regiochemical directing effects of the phosphonate moiety are uncertain. In addition, only limited examples of intramolecular oxa-Michael reactions of vinyl phosphonates have been reported in the literature.[7a,13]

Dienes **7a–c** were prepared via an olefination (Horner–Wadsworth–Emmons) reaction between the appropriate aldehyde and tetraethyl methylene diphosphonate (Scheme 3).[14] Diene **7d** was prepared following literature precedent by silylation of unsaturated ketone **8**.[15,16]

Scheme 3. Synthesis of the Dienes



The reaction of 3-methyl diene **7a** with benzaldehyde under the standard Mori–Tamaru conditions ($Ni(acac)_2$, BEt_3, THF, room temperature, 36 h) resulted in the formation of the expected vinyl phosphonate **9a** in 45% isolated yield (Scheme 4 and Table 1, entry a). Reactions with other aromatic and aliphatic aldehydes (entries b–g) were also successful.

Scheme 4. Mori–Tamaru Reaction of Diene 7a

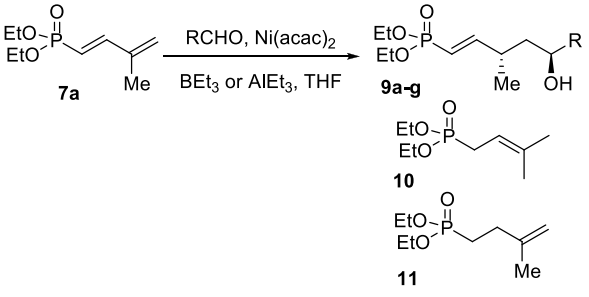


Table 1. Mori–Tamaru Reaction of Diene 7a Using BEt_3 or $AlEt_3$

		yield of **9** (%)	
entry	aldehyde (R)	with BEt_3[a]	with $AlEt_3$[b]
a	Ph	45	72
b	ethyl	41	65
c	2-furyl	26	63
d	2-thiophenyl	48	59
e	2-naphthyl	47	61
f	4-fluorophenyl	36	60
g	4-hydroxyphenyl	17	0

[a]BEt_3 (1 M in THF, 2.6 equiv), $Ni(acac)_2$ (0.1 equiv), RCHO (2 equiv), THF, rt, 36 h. [b]$AlEt_3$ (1 M in hexane, 3.5 equiv), $Ni(acac)_2$ (0.36 equiv), RCHO (3.5 equiv), THF, −50 to 0 °C, 5 h.

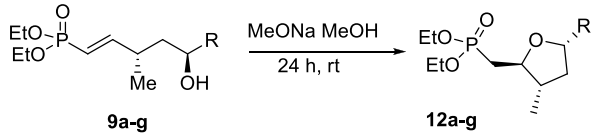
However, the isolated yields were lower than desired. The reaction was complicated by the formation of byproducts, typically in a ratio of 3:1:2 (**9**:**10**:**11**). The byproducts were isolated and identified as alkenes **10** and **11**.[17] We speculated that these compounds were the products of diene reduction, presumably by nickel hydrides formed by decomposition of the catalyst later in the reaction.

We postulated that a faster reaction between the diene and aldehyde would lead to a reduction in byproduct formation. We examined additional alkylmetal reagents that might lead to a more rapid transfer of the alkyl group or improved activation of the aldehyde, ultimately leading to a faster homoallylation reaction. We were pleased to observe that replacing BEt_3 with $AlEt_3$ resulted in faster reaction. The ratio of products (**9**, **10**, and **11**) had improved to 10–40:2:1, resulting in improved isolated yields of the desired vinyl phosphonates **9** (Table 1).

In all cases (BEt_3 or $AlEt_3$), nitrogen-containing heterocyclic aldehydes (*N*-methylindole-3-carboxaldehyde, *N*-methylpyrrole carboxaldehyde, and pyridine carboxaldehyde) and unsaturated aldehydes (crotonaldehyde and ethyl *trans*-2-oxo-2-butanoate) failed to react.

Treatment of vinyl phosphonates **9a–g** with sodium methoxide in methanol resulted in cyclization, yielding tetrahydrofurans **12a–g** (Table 2). In all cases, the

Table 2. Cyclization of Vinyl Phosphonates 9



entry	substituent (R)	yield (%)
a	Ph	85
b	ethyl	55
c	2-furyl	62
d	2-thiophenyl	89
e	2-naphthyl	85
f	4-fluorophenyl	75
g	4-hydroxyphenyl	36

diastereoselectivity in the cyclization was >95%. X-ray crystal structure determination of **12g** allowed the assignment of the relative stereochemistry of the ring substituents (see the Supporting Information). Treatment of **9a** with sodium hydride in THF also resulted in cyclization to give **12a** in similar yield and diastereoisomeric ratio. Other bases were

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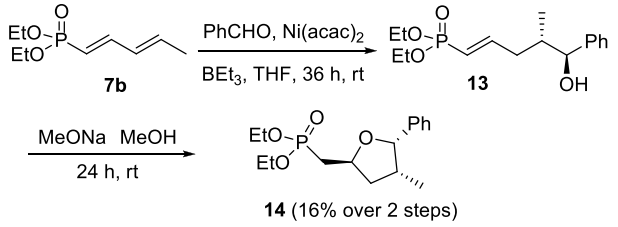
either ineffective (Et_3N or iPr_2NEt in CH_2Cl_2) or resulted in complex mixtures (tBuOK in THF, DBU in CH_2Cl_2).

The reaction of diene **7b** with benzaldehyde was much slower than that with **7a** and was complicated by significant byproduct formation (Scheme 5). Vinyl phosphonate **13** was

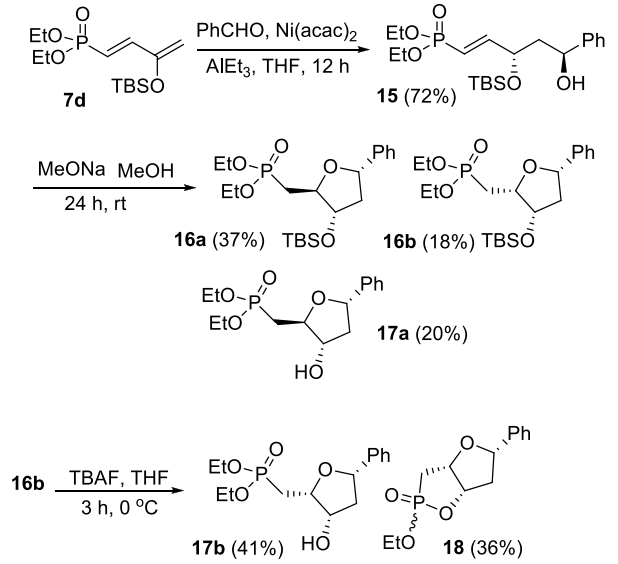
Scheme 5. Mori–Tamaru Reaction of Diene 7b with Benzaldehyde



difficult to isolate by column chromatography. Treatment of the impure vinyl phosphonate **13** with sodium methoxide in methanol resulted in cyclization to yield tetrahydrofuran **14** in 16% isolated yield over two steps. Unfortunately, the reaction of diene **7c** with benzaldehyde failed to yield any vinyl phosphonate.

Although the 4-methyl- and 4-OBn-substituted dienes **7b** and **7c** showed a lack of reactivity, we were pleased to observe that reaction of the 3-OTBS-substituted diene **7d** with benzaldehyde successfully produced vinyl phosphonate **15** in 72% isolated yield (Scheme 6). Treatment of vinyl

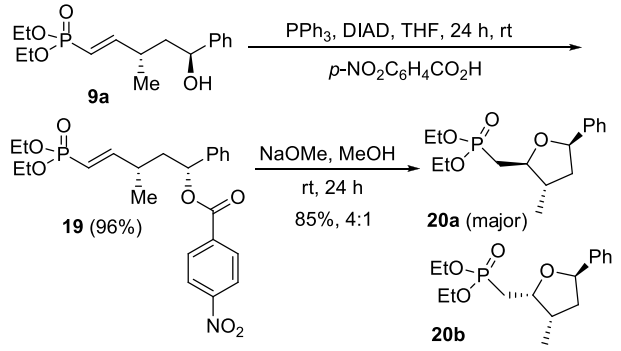
Scheme 6. Mori–Tamaru Reaction of Diene 7d with Benzaldehyde



phosphonate **15** with sodium methoxide in methanol resulted in cyclization to yield tetrahydrofurans **16a**, **16b**, and **17a** in 75% combined isolated yield. Since alcohol **17** arises by in situ deprotection of **16a**, the overall diastereoselectivity for the cyclization is 3:1. Alcohol **17a** is also formed when tetrahydrofuran **16a** is treated with TBAF in THF. In contrast, treatment of the isomeric tetrahydrofuran **16b** with TBAF in THF led to the formation of a 1:1 mixture of alcohol **17b** and phostone **18**. Since cyclization is more easily achieved when the hydroxyl and phosphonate are in a *cis* relationship, this experiment provides confirmation of the assigned relative stereochemistry.

The Mitsunobu reaction[18,19] of **9a** using *p*-nitrobenzoic acid as the nucleophile proceeded smoothly to give *p*-nitrobenzoate ester **19** in high yield with clean inversion of the stereochemistry (Scheme 7). Treatment of ester **19** with sodium

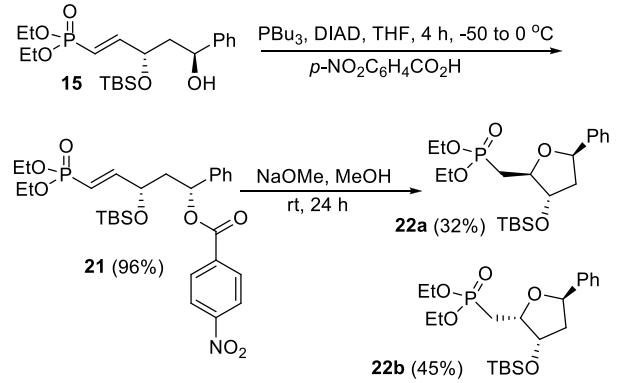
Scheme 7. Mitsunobu Reaction and Cyclization with (Methyl) Vinyl Phosphonate 9a



methoxide in methanol resulted in both ester methanolysis and in situ cyclization to give an inseparable mixture of tetrahydrofuran diastereoisomers **20a** and **20b** in a 4:1 ratio.

In contrast, the Mitsunobu reaction with OTBS-substituted vinyl phosphonate **15** required some modifications to the reaction conditions (Scheme 8).[19] Using tributylphosphine in

Scheme 8. Mitsunobu Reaction and Cyclization with (OTBS) Vinyl Phosphonate 15



place of triphenylphosphine resulted in the formation of *p*-nitrobenzoate **21** in excellent yield with clean inversion of the stereochemistry. Treatment with sodium methoxide in methanol again led to methanolysis and in situ cyclization to give a 1:1.5 mixture of diastereoisomeric tetrahydrofurans **22a** and **22b** in 77% yield.

Deprotection of the TBS group with TBAF allowed assignment of the relative stereochemistry of the ring substituents in compounds **22a** and **22b** (Scheme 9). Reaction of the *trans* isomer **22a** with TBAF in THF resulted in the formation of alcohol **23a**. In contrast, deprotection of the *cis* isomer **22b** led to in situ cyclization, giving a 1:1 mixture of diastereoisomeric phostones **24** along with a small amount of alcohol **23b**, confirming the assigned relative stereochemistry.

In conclusion, we have shown that the Mori–Tamaru reaction of phosphono-substituted dienes is an efficient route to methylene phosphonate-substituted tetrahydrofurans. Nick-

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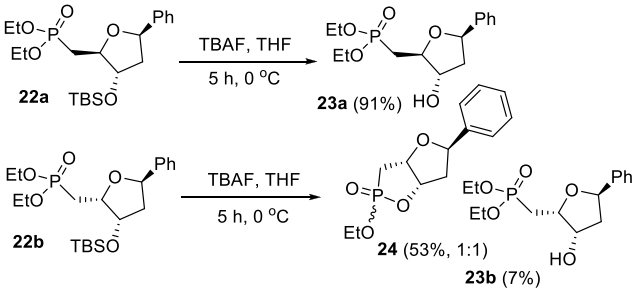
Scheme 9. Deprotection of OTBS-Protected Tetrahydrofurans 22a and 22b



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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01080.

Experimental procedures; ^{1}H, ^{13}C, and ^{31}P NMR spectra for all compounds; and X-ray crystallographic data (PDF)

Accession Codes

CCDC 1983928 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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