The Preparation of Trisubstituted Alkenyl Nucleoside Phosphonates under Ultrasound-Assisted Olefin Cross-Metathesis

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Intermolecular ultrasound-assisted olefin cross-metathesis is reported. This approach allows an easy access to challenging trisubstituted alkenyl nucleoside phosphonates. Regioselective chemoenzymatic deacetylation and Mitsunobu coupling are also described.

Acyclic nucleoside phosphonates (ANPs), pioneered by Holý and De Clercq, represent an important class of antivirals.¹ Among these, (*S*)-1-(3-hydroxy-2-phosphonomethoxypropyl)cytosine (HPMPC, Cidofovir), 9-(2-phosphonylmethoxyethyl)adenine (PMEA, Adefovir), and (*R*)-9-(2-phosphonomethoxypropyl)-adenine (PMPA, Tenofovir) are approved for the treatment of human cytomegalovirus, hepatitis B, and HIV infections, respectively. As a result, the synthesis and biological evaluation of a large panel of ANPs, including derivatives with unsaturated side chains,² have been systematically investigated.³

Recently, we have reported a new family of ANPbearing (*E*)-4-phosphono-but-2'en-1'-yl side chain⁴ in which the oxygen heteroatom has been replaced by a *trans*

(2) (a) Choo, H.; Beadle, J. R.; Kern, E. R.; Prichard, M. N.; Keith, K. A.; Hartline, C. B.; Trahan, J.; Aldern, K. A.; Korba, B. E.; Hostetler, K. Y. *Antimicrob. Agents Chemother.* **2007**, *51*, 2611. (b) Harden, M. R.; Parkin, A.; Parratt, M. J.; Perkins, R. M. J. Med. Chem. **1993**, *36*, 1343.

(3) Krečmerová, M. In *Herpesviridae – A look into this unique family of Viruses*; Magel, G. D., Ed.; InTech: Rijeka, 2012; pp 245–270.

(4) Kumamoto, H.; Topalis, D.; Broggi, J.; Pradère, U.; Roy, V.; Berteina-Raboin, S.; Nolan, S. P.; Deville-bonne, D.; Andrei, G.; Snoeck, R.; Garin, D.; Crance, J.-M.; Agrofoglio, L. A. *Tetrahedron* 2008, 64, 3517.

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double bond. We have shown that this modification allows mimicry of the three-dimensional geometry provided by the backbone of ANP.⁵ Herein we report on the extension of this methodology to trisubstituted alkenyl acyclic nucleoside derivatives (Figure 1).



Figure 1. Structure of some ANPs and targeted compounds.

The preparation of stereodefined trisubstituted alkenes is exceedingly important in view of the biological activity of these molecules. Numerous synthetic approaches have been devised to access such architectural motifs, generally through a Wittig olefination⁶ or from boration,⁷

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^{(1) (}a) De Clercq, E.; Holý, A. *Nat. Rev. Drug Discovery* **2005**, *4*, 928. (b) De Clercq, E. *Antiviral Res.* **2007**, *75*, 1.

⁽⁵⁾ Topalis, D.; Pradere, U.; Roy, V.; Caillat, C.; Azzouzi, A.; Broggi, J.; Snoeck, R.; Andrei, G.; Lin, J.; Eriksson, S.; Alexandre, J. A. C.; El-Amri, C.; Deville-Bonne, D.; Meyer, P.; Balzarini, J.; Agrofoglio, L. A. *J. Med. Chem.* **2011**, *54*, 222.

bromoboration,⁸ iodination⁹ of alkynes or haloalkynes, and olefin cross-metathesis (CM).¹⁰ However, the formation of a trisubstituted hindered alkene system through simple CM exhibits low yields possibly due to steric congestion, the olefin, or catalyst's poor reactivity requiring a moderately high catalyst loading and elevated reaction temperatures. To address some of these issues, we now report on the effect of ultrasound-assisted olefin CM for the preparation of challenging trisubstituted alkenyl nucleoside phosphonates.

Our retrosynthetic approach is depicted in Scheme 1. The target compounds could be obtained from the (Z)-monoacetyl derivative 8 under Mitsunobu conditions with either a purine or pyrimidine moiety. Compound 8 could be prepared by regioselective lipase-catalyzed hydrolysis of diacetyl derivative 6 obtained through a cross-metathesis reaction between olefin 4 and dimethyl allylphosphonate.

Scheme 1. Retrosynthetic Scheme to New ANPs Derivatives



Compound 4 was prepared by a new chemoenzymatic route starting from glycerol 1 or 2-methylene-1,3-propanediol 5, which represents an attractive alternative to previously reported approaches¹¹ (Scheme 2). The regioselective lipase-catalyzed acetylation of inexpensive glycerol 1 gave the diacetate 2 in 95% isolated yield.¹²



(6) (a) Burke, S. D.; Hong, J.; Lennox, J. R.; Mongin, A. P. J. Org. Chem. **1998**, 63, 6952. (b) Breit, B.; Zhan, S. K. Angew. Chem., Int. Ed. **1999**, 38, 969.

(7) Brown, H. C.; Bhat, N. G. J. Org. Chem. 1988, 53, 6009.

(8) (a) Wang, C.; Tobrman, T.; Xu, Z.; Negishi, E.-I. Org. Lett. **2009**, *11*, 4092. (b) Negishi, E.-I.; Tobrman, T.; Rao, H.; Xu, S.; Lee, C.-T. Isr. J. Chem. **2010**, *50*, 696.

- (9) Chen, Z.; Jiang, H.; Li, Y.; Qi, C. Chem. Commun. 2010, 46, 8049.
 (10) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. Org. Lett. 2002, 11, 1939.
- (11) Shintani, R.; Moriya, K.; Hayashi, T. Chem. Commun. 2011, 47, 3057.

(12) Magnusson, C. D.; Haraldsson, G. G. Tetrahedron 2010, 66, 2728.

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Compound 2 was then subjected to an oxidation reaction under several conditions, in the presence of 2,2,6,6tetramethylpiperidine-1-oxyl (TEMPO),¹³ 2-azaadamantane-N-oxyl (AZADO),¹⁴ and 2-iodoxybenzoic acid (IBX).¹⁵ The use of IBX offered the best result, affording ketone 3 in almost quantitative yield. Olefin 4 was synthesized from ketone 3 with PPh₃MeBr under Wittig conditions in an excellent 93% yield.

Based on the general model for selectivity in olefin crossmetathesis proposed by Grubbs et al.,¹⁶ we investigated the selective CM between dimethyl allylphosphonate (6) (Type I) with less reactive 1,1-disubstituted olefin 4 (Type III). Considering that type III olefins are unable to homodimerize, we decided to carry out this reaction with a stoichiometric excess (2 equiv) of 1,1-disubstituted olefin 4, as the use of a larger excess does not improve the conversion.

Table 1. Optimized Conditions for RCM^a



| entry | catalyst(mol~%) | solvent | time (h) | $7 \ (\%)^e$ | |
|--------|----------------------------------|------------|----------|--------------|--|
| 1^b | 1 	imes 5%-[Ru]-I | CH_2Cl_2 | 24 | 9 | |
| 2^b | 1	imes5%-[Ru]-II | CH_2Cl_2 | 24 | 16 | |
| 3^b | 3	imes5%-[Ru]-I | CH_2Cl_2 | 24 | 23 | |
| 4^b | 3	imes5%-[Ru]-I | DCE | 24 | 32 | |
| 5^c | 1 	imes 10%-[Ru]-I | CH_2Cl_2 | 4 | 38 | |
| 6^c | $1 \times 10\%$ -[Ru]- II | CH_2Cl_2 | 4 | 70 | |
| 7^d | 3	imes5%-[Ru]-I | CH_2Cl_2 | 20 | 92 | |
| 8^d | 3 	imes 3%-[Ru]-I | CH_2Cl_2 | 20 | 90 | |
| 9^d | 3	imes 2%-[Ru]-I | CH_2Cl_2 | 20 | 86 | |
| 10^d | 3	imes 2%-[Ru]-II | CH_2Cl_2 | 20 | $93(89)^{f}$ | |
| 11^d | 1	imes5%-[Ru]-I | CH_2Cl_2 | 20 | 49 | |
| 12^d | 3	imes1%-[Ru]-I | CH_2Cl_2 | 20 | 76 | |

^{*a*} All reactions were performed with 1.0 equiv of dimethyl allylphosphonate and 2.0 equiv of olefin **4** in solvent (0.1 M). ^{*b*} Reactions performed under classical thermal conditions at 40 °C. ^{*c*} Reactions performed under microwave irradiation at 100 °C. ^{*d*} Reactions performed under ultrasound at 55 °C. ^{*e*} Conversion determined by ¹H NMR. ^{*f*} Isolated yield.

The reaction was performed at 40 °C in degassed CH_2Cl_2 under classical heating in the presence of 5 mol % of "second generation" catalysts [Ru]-I¹⁷ (Nolan–Grubbs)

- (13) De Nooy, A. E.; Besemer, A. C.; Van Bekkum, H. Synthesis 1996, 1153.
- (14) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. J. Am. Chem. Soc. 2006, 128, 8412.
- (15) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. J. Org. Chem. 1995, 60, 7272.
- (16) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. J. Am. Chem. Soc. **2003**, 125, 11360.
- (17) Huang, J.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. J. Am. Chem. Soc. 1999, 121, 2674.

and [Ru]-II¹⁸ (Hoveyda–Grubbs) (Table 1, entries 1 and 2). The reaction was monitored by TLC and ¹H NMR and showed the rapid formation and accumulation of homodimer 7' which does not undergo a secondary metathesis reaction with Type III olefin 4 to give the expected crosscoupling product. After 24 h, both catalysts showed their limitations for CM with only 4% of conversion and a high amount of homodimer 7' detected by ¹H NMR and TLC. Unfortunately, no improvement was observed when using a catalyst loading as high as 15 mol % (added in three equal portions, entries 3 and 4).

We then turned our attention to microwave irradiation¹⁹ (entries 5 and 6), which has resulted in many cases in a short reaction time, a low loading of catalyst, and a higher yield compared with classical thermal conditions.²⁰ In our hands, CM under microwave irradiation at 100 °C in DCE with 10 mol % [Ru]-II gave 70% (entry 6) conversion after 4 h while [Ru]-I gave a modest 38% yield (entry 5). Noteworthy, under these conditions, larger amounts of impurities were formed, probably due to the more significant thermal decomposition of the ruthenium complex that leads to tedious purification.

Ultrasound applications have been recently reported for latent [Ru] metathesis catalyst activation containing N-heterocyclic carbene ligands (NHC) in ROMP.²¹ Thus, we investigated the effects of ultrasound irradiation in CM and we found that its use had a positive influence on the conversion. In fact, sonication at 55 °C of the reaction mixture with 15 mol % [Ru]-I (added in three equal portions) permitted reaching a 92% conversion (entry 7). The catalyst loading was then gradually decreased from 15 mol % [Ru]-I to 3 mol % [Ru]-I to determine the optimal loading. Surprisingly, no significant decrease was observed in the conversion until 6 mol % [Ru]-I with 86% (entry 9). When the more reactive catalyst [Ru]-II was used at this loading, a 93% conversion was obtained (entry 10). Even under ultrasonication, the sequential catalyst addition was critical. In fact, when the reaction was carried out following one addition of 5 mol % [Ru]-I, only 49% of product was detected (entry 11). Finally, it should be noted that the conversion was stopped if sonication was suspended. We therefore hypothesized the following (Scheme 3): (1) The mechanical force brought by ultrasonication could potentially enhance the ligand dissociation of the latent precatalyst (a) to generate the active species (b); (2) the "degassing effect" of ultrasounds permits efficient expulsion of the ethylene gas generated during the reaction avoiding the regeneration of the terminal olefin (cycle I). In many cases, removal of ethylene was found to be essential for achieving high conversions;²² (3) the sonication permits the less reactive homodimer to react

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Scheme 3. Proposed Catalytic System for Ultrasound Olefin CM^a



 a Ligand dissociation (from **a** to **b**); formation of homodimer (cycle I); formation of desired heterodimer (cycle II).

toward the formation of the desired product (cycle II). Thus, the use of ultrasonication offers a very effective protocol leading to trisubstituted olefins *via* CM using either [Ru]-I and [Ru]-II catalysts.

Diacetate **6** was then subjected to the lipase catalyzed hydrolysis of the targeted *trans* acetyl group (Table 2).



| entry | $lipase^b$ | time (h) | 8 (%) ^c | 9 (%) ^c | 10 (%) ^c |
|-------|------------|----------|---------------------------|---------------------------|----------------------------|
| 1^c | PPL | 24 | 21 | 41 | traces |
| 2^c | Amano PS | 48 | 32 | 33 | traces |
| 3^c | CAL-B | 16 | 83 | 0 | 11 |

^{*a*} Reactions were performed with diacetate 7 in 0.1 M phosphate buffer pH 7.0 and appropriate lipase (100% w/w). ^{*b*} Porcine Poncreas lipase (PPL), *Burkholderiacepacia* lipase (Amano PS), *Candida antarctica* lipase B (CAL-B). ^{*c*} Isolated yield.

Takabe,²³ Imai,²⁴ and Deska²⁵ have already reported several examples of desymmetrization of prochiral diols

⁽¹⁸⁾ Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. J. Am. Chem. Soc. 2000, 122, 8168.

⁽¹⁹⁾ Fuwa, H.; Noto, K.; Sasaki, M. Org. Lett. 2010, 12, 1636.

⁽²⁰⁾ Coquerel, Y.; Rodriguez, J. Eur. J. Org. Chem. 2008, 7, 1125.

 ^{(21) (}a) Jakobs, R. T. M.; Sijbesmas, R. P. *Organometallics* 2012, *31*, 2476.
 (b) Piermattei, A.; Karthikeyan, S.; Sijbesma, R. P. *Nat. Chem.* 2009, *1*, 133–137.

⁽²²⁾ Pietraszuk, C.; Marciniec, B.; Fischer, H. Organometallics 2000, 19, 913–917.

⁽²³⁾ Hisano, T.; Onodera, K.; Toyabe, Y.; Mase, N.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2005**, *46*, 6293.

⁽²⁴⁾ Miura, T.; Umetsu, S.; Kanamori, D.; Tsuyama, N.; Jyo, Y.; Kawashima, Y.; Koyata, N.; Murakami, Y.; Imai, N. *Tetrahedron* **2008**, *64*, 9305.

Scheme 4. Mitsunobu Conditions^a



^{*a*} Reactions were performed using nucleobase, monoacetate **8** (1.5 equiv), PPh₃ (1.5 equiv), DIAD (1.5 equiv) in THF (0.05 M) at 70 °C during 20 h under N_2 .

using porcine pancreas lipase (PPL) with excellent selectivity. Unfortunately, in our case, poor selectivity and slow conversion were observed using either PPL or Burkholderiacepacia lipase (Amano Lipase PS, Sigma-Aldrich). In fact, PPL gave a mixture of isomers 8 (major) and 9 (minor) (Table 2, entry 1). Using Amano PS gave the desired regioisomer 8 in approximately equal proportion with *E*-isomer 9 (entry 2). Dideprotected byproduct 10 was detected only as traces using both PPL and Amono PS. However, when *Candida antarctica* lipase B (CAL-B) was used, the hydrolysis took place rapidly with excellent selectivity toward the *trans* acetyl group giving monoacetate 8 in 83% yield in only 16 h (entry 3) and no trace of E-isomer was detected. In addition, the high reactivity of this lipase led also to 11% of diol 10. The structures of both isomer 8 and 9 were clearly determined by NOESY experiments.

Compound 8 was then reacted under Mitsunobu conditions with several previously N(Bz) or N(Boc) protected pyrimidine and purine bases in the presence of PPh₃ and DIAD in THF at 70 °C to afford the coupling product 11–16 with satisfactory yields (Scheme 4).²⁶ The N^9 alkylation for purine derivatives 15 and 16 has been confirmed by HMBC experiments.

The reaction of **11** or **12** with NH₃/MeOH or K₂CO₃/ MeOH did not provide the expected acyl deprotection but a diene derivative resulting from the 1,4-elimination of the α -phosphorus acidic proton and Ac group. We thus turned our attention to enzymatic hydrolysis. However, neither CAL-B nor PPL gave satisfactory results at neutral pH. Finally, compounds **11** and **12** were deprotected using *para*-toluene sulfonic acid (*p*TSA) in refluxing MeOH to afford **17** and **18**, respectively. Although the allylic acetate is rapidly cleaved, the modest yield is due to the stability of Scheme 5. Deprotection under Acidic Conditions



the benzoyl group under acidic conditions (Scheme 5). N(Boc)-protected derivatives were more easily dideprotected using methanolic 1 M HCl affording **19–21** in good yields. The 6-chloropurine derivative **16** was converted to hypoxanthine **22** using aqueous formic acid. Methylphosphonates were then converted to phosphonic acids by treatment with bromotrimethylsilane in the presence of 2,6-lutidine to avoid bromination of the free methylhydroxy group (not described).²⁷

In conclusion, this is the first preparation of trisubstituted alkenyl nucleoside phosphonates using an ultrasoundassisted olefin cross-metathesis, regioselective chemoenzymatic deacetylation, and Mitsunobu coupling sequence. The antiviral evaluation of the phosphonic acid form of these new ANPs will be reported in due course.

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Supporting Information Available. Experimental procedures, supplementary data, compound characterization, and NMR charts. This material is available free ofcharge via the Internet at http://pubs.acs.org.

⁽²⁵⁾ Sapu, C. M.; Bäckvall, J.-E.; Deska, J. Angew. Chem., Int Ed. 2011, 50, 9731.

⁽²⁶⁾ Pradère, U.; Roy, V.; Montagu, A.; Sari, O.; Hamada, M.; Balzarini, J.; Snoeck, R.; Andrei, G.; Agrofoglio, L. A. *Eur. J. Med. Chem.* **2012**, *57*, 126.

⁽²⁷⁾ Hocková, D.; Holý, A.; Masojídková, M.; Keough, D. T.; Jersey, J. D.; Guddat, L. W. *Bioorg. Med. Chem.* **2009**, *17*, 6218.

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