Tetrahedron Letters 49 (2008) 4329–4332

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Pummerer-type reactions in the (2-methylsulfanyl-2-phosphonyl) thiopyran 1-oxide series

Mickael Denancé, Remi Legay, Annie-Claude Gaumont, Mihaela Gulea *

Laboratoire de Chimie Moléculaire et Thio-Organique, ENSICAEN, Université de Caen Basse-Normandie, CNRS, 6 Boulevard du Maréchal Juin, 14050 Caen, France

ARTICLE INFO

Article history:
Received 16 April 2008
Revised 28 April 2008
Accepted 7 May 2008
Available online 10 May 2008

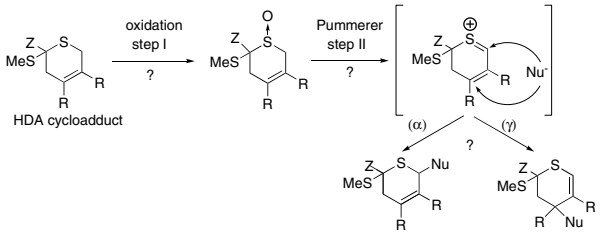
Keywords:
Pummerer reaction
Chemoselective sulfoxidation
Thiopyrans
Sulfoxides
Phosphonates

ABSTRACT

Two (3,6-dihydro-2-methylsulfanyl-2*H*-thiapyran-2-yl)phosphonate derivatives have been chemoselectively oxidized on the thiopyran sulfur. The obtained allylic six-membered cyclic sulfoxides **2a** and **2b** were reacted under Pummerer reaction conditions leading to new thiopyran derivatives (**4a** and **6b**, respectively). In both studied cases, the nucleophilic attack of β,γ-unsaturated thionium ion intermediate took place regioselectively at the γ-position (even when occupied by a methyl substituent like in **2b**). An unexpected second product **7b** was however obtained from substrate **2b** (having the dimethyl-substituted double bond). Dephosphorylation of **7b** under basic conditions led to an original conjugated tri-unsaturated trifluromethylcarbonyl thiopyran product (**8b**). These results represent new original examples of the Pummerer reaction.

The Pummerer reaction represents a useful synthetic tool in organic chemistry. Several book chapters[1] and reviews[2] deal with this reaction, including various synthetic applications, as well as mechanistic studies. Among the various sulfoxides used as substrates in Pummerer-type reactions, six-membered cyclic sulfoxides are of particular interest for synthetic applications targeting biomolecules (see e.g., thiaglycosides,[3] thianucleosides,[4] cephalosporins,[5] antibacterial agents[6]). Earlier studies of our laboratory dealt with the use of dithioesters as dienophiles in hetero-Diels–Alder (HDA) reactions,[7] which allowed a convenient access to highly functionalized thiopyrans, either by using appropriate functionalized dienes, or by subsequent functionalization of the cycloadduct double bond. Taking advantage of the presence of sulfur atom, the Pummerer reaction could be a complementary original route to introduce new functions on these structures. From a theoretical point of view, the Pummerer reaction involving an allylic sulfoxide (Scheme 1, step II) should proceed via a β,γ-unsaturated thionium ion intermediate, which could be attacked by the nucleophile at either the α- or γ-position.[2g,8,9] It is still not established however which are the factors governing the regioselectivity in this type of reaction. Moreover, our substrates are six-membered cyclic allylic sulfoxides, which represent a particular case, since in some examples of similar substrates, the Pummerer reaction led to abnormal or unexpected products.[10] To study this reaction, a first condition is however required: the chemoselective oxidation of the thiopyran sulfur, since the exocyclic sulfur from the methylsulfanyl group is also a reactive site (Scheme 1, step I). Some studies dealing with the relative nucleophilicity of the two sulfur atoms in 1,5-dithioglycoside systems have already been reported.[11] In a recent paper, it was shown that in the electrophilic S-oxidation (with mCPBA) of 1,5-dithioglycopyranosides, the *endo* sulfoxide is obtained preferentially, demonstrating that the endocyclic sulfide is more nucleophilic than the exocyclic one.[8d] Concerning the dithiopyrane adducts, previous studies in our group also support this conclusion. Hence, the desulfanylation under radical conditions (using Bu_3SnH/AIBN system) of these compounds was totally selective, with the attack of the tributyltin radical on the more electrophilic exocyclic sulfur atom.[7] These results led us to suppose that the desired *endo* sulfoxide should be obtained.

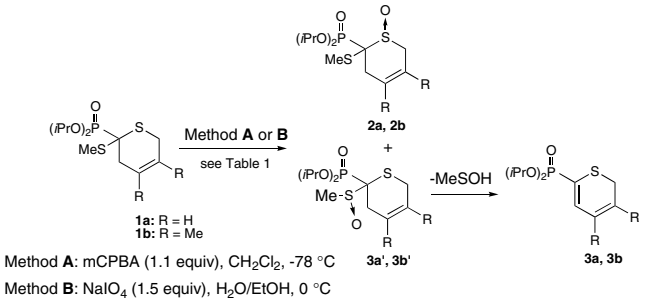
This Letter describes our preliminary results obtained in the selective S-oxidation and Pummerer reaction tested on two substrates, **1a** and **1b** (Scheme 2), readily prepared by HDA reaction following the protocol described by Masson and co-workers[7a]



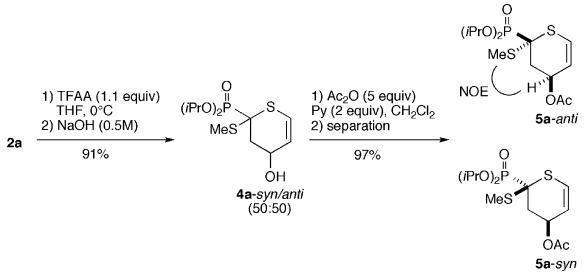
Scheme 1.

* Corresponding author.
E-mail address: mihaela.gulea@ensicaen.fr (M. Gulea).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.032



Scheme 2.



Scheme 3.

between a phosphonodithioformate and butadiene or 2,3-dimethyl butadiene, respectively. The substrates were selected to have in the cycloadduct either an unsubstituted (**1a:** R = H) or a disubstituted double bond (**1b:** R = Me).

First, the reactivity of 2-methylsulfanyl-2-phosphonyl dihydrothiopyrans **1a** and **1b** toward oxidation was examined. Classical sulfoxidation conditions were tested (mCPBA in CH_2Cl_2 and $NaIO_4$ in $EtOH/H_2O$, at different temperatures between −78 °C and rt). In all the cases, the desired sulfoxides **2a** and **2b** were mainly obtained together with a secondary product **3a** or **3b**, respectively, resulting very probably from elimination of methylsulfenic acid (MeSOH) from the methylsulfoxide regioisomer **3a**′ or **3b**′ (Scheme 2, Table 1). The ratio between **2** and **3** reflects in this case the *endo*/*exo* selectivity of the sulfur oxidation. In both cases, it was possible to separate products **2** and **3** from the reaction mixture by chromatography on silica gel. For the substrate **1a** the best isolated yield in product **2a** (83%) was obtained using Method **A** (Table 1).[12] In these reaction conditions, **2a** was obtained as a mixture of two diastereomers in a 93:7 ratio. In the case of **1b**, Method **B** led to the best yield (65%) in product **2b**, which was obtained as a mixture of two diastereomers in a 65:35 ratio.

These results represent a supplementary evidence of the endo- versus exocyclic sulfur reactivity in dithiopyran series.

Then, 2-methylsulfanyl-2-phosphonyl dihydrothiopyran 1-oxide **2a** was reacted under Pummerer reaction conditions with trifluoroacetic anhydride (TFAA), leading to allylic alcohol **4a** in 91% yield, after treatment of the reaction mixture with a NaOH aqueous solution (Scheme 3). Under these conditions, the Pummerer reaction took place regioselectively, with the nucleophilic attack at the γ-position of the β,γ-unsaturated thionium ion (see Scheme 1). No trace of the compound resulting from nucleophilic attack in the α-position was observed. Concerning the diastereoselectivity of the reaction, the starting sulfoxide **2a** having a high diastereomeric excess (86% de), led however to product **4a** as an equimolar mixture of *syn*/*anti* diastereomers. Very probably, phosphonyl and methylsulfanyl groups are too far from the reactive center to influence the diastereoselectivity of the nucleophilic addition. Acetylation of alcohol **4a** led to a mixture of the corresponding diastereomeric acetates **5a**-*syn* and **5a**-*anti*, which were separated by chromatography on silica gel. It was then possible to assign their relative configuration using NMR experiments.

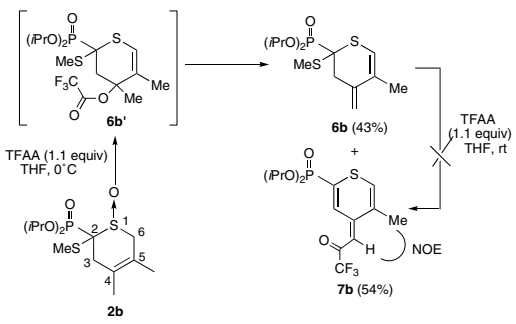
Compared to the first studied case, the second selected substrate **2b** has the double bond 1,2-disubstituted with two methyl groups. We expected that this modification would limit the nucleophilic attack at the more hindered γ-position of the β,γ-unsaturated thionium ion and favor attack at the α-position (see Scheme 1). Reacted under Pummerer conditions[13] defined previously, sulfoxide **2b** led to two products in quasi equimolecular ratio (Scheme 4). The first product was easily identified by NMR as compound **6b**. This product very probably results from a trifluoroacetate elimination from **6b**′, which was formed by the nucleophilic attack of the trifluoroacetate anion at the γ-position of the thionium ion intermediate (like in the previous case **2a**→**4a**), in spite of the presence of the methyl group in this position.

Concerning the second product, a series of NMR experiments was performed to ensure its identification and finally structure **7b** was assigned.[14] In order to propose a reasonable mechanism for its formation, we first checked if compound **7b** was originated from compound **6b** by treating this latter with 1.1 equiv of TFAA, but no trace of **7b** was obtained. However, when sulfoxide **2b** was treated with an excess of TFAA (3 equiv) the same mixture of products **6b**/**7b** was obtained in a 1:1 ratio. The formation of the exocyclic and the $C^5{=}C^6$ double bonds can be explained by a mechanism similar to that proposed for **6b**, and the $C^2{=}C^3$ double bond can be formed by a thiophilic attack of the trifluoroacetate nucleophile on the methylsulfanyl group followed by a subsequent β-elimination. However, the introduction of the trifluoroacetyl group on the exocyclic double bond remains unclear. It is worth noting that a quite similar example was already reported in the literature, in which a trifluoroacetyl group was also unexpectedly introduced by a Pummerer reaction α- to the sulfur, in a dihydrothiazine ring system.[6] No explanation was given. Finally, in order to access new tri-unsaturated conjugate thiopyran systems, which

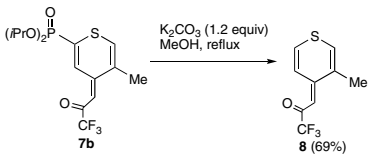
Table 1
Sulfoxidation of substrates **1a** and **1b**

Substrate	Method	Product **2** (Yield %)[a]	Product **3** (Yield %)[a]	^{31}P NMR, δ (ppm) **2** Major/**2** minor/**3** dr[b]
1a	**A**	**2a** (83) 93:7	**3a** (13)	17.2/16.2/12.3
1a	**B**	**2a** (80) 75:25	**3a** (11)	17.2/16.2/12.3
1b	**A**	**2b**[c]	**3b**[c]	—[c]
1b	**B**	**2b** (65) 65:35	**3b** (12)	17.4/16.8/12.5

[a] Isolated yield.
[b] Diastereomeric ratio **2** major/**2** minor determined by ^{31}P NMR.
[c] **2b** and **3b** were detected by ^{31}P NMR (~1:1 ratio) in a complex reaction mixture and were not isolated.



Scheme 4.



Scheme 5.

can be interesting conjugated substrates for reactivity studies, we attempted to cleave the phosphoryl group in compound **7b**. Under basic conditions (potassium carbonate in refluxing methanol), dephosphorylation occurred easily leading to product **8** in 60% yield (Scheme 5).[15]

In conclusion, we have succeeded in oxidizing chemoselectively the thiopyran sulfur in the presence of an exocyclic methylsulfanyl group in the 2-position in the case of two selected substrates. The obtained thiopyran 1-oxides, which are six-membered cyclic allylic sulfoxides, were reacted under Pummerer reaction conditions leading to new thiopyran derivatives. In both studied cases **2a** and **2b** (with an unsubstituted and with a 1,2-dimethyl substituted double bond, respectively), the nucleophilic attack on the β,γ-unsaturated thionium ion intermediate took place regioselectively at the γ-position, even when occupied by a methyl substituent, leading to **4a** and **6b**, respectively. An unexpected side-product **7b** having an original conjugated tri-unsaturated trifluromethylcarbonyl thiopyran structure was however obtained from substrate **2b**. The mechanism of the formation of this compound remains unclear. Cleavage under basic conditions of the phosphoryl group in **7b** leads to another original compound **8b**. Mechanistic studies and possible synthetic applications of these Pummerer-type reactions are currently under investigation in our laboratory.

Acknowledgments

We gratefully acknowledge the 'Ministère de la Recherche et des Nouvelles Technologies', the CNRS, the Région Basse-Normandie, and the European Union (FEDER funding) for financial support. Authors thank Karine Jarsalé (University of Caen) for the high-resolution mass analysis.

References and notes

1. Books: (a) Marino, J. P. In *Topics in Sulfur Chemistry*; Senning, A., Ed.; George Thieme: Stuttgart, Germany, 1976; Vol. 1, pp 1–110; (b) Oae, S. Organic Chemistry of Sulfur. In Oae, S., Ed.; Plenum: New York, NY, 1977; pp 383–471; (c) Grierson, D. S.; Husson, H. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergammon: Oxford, 1991; Vol. 6, pp 909–947; (d) Kennedy, M.; McKervey, M. A.. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergammon: Oxford, 1991; Vol. 7, pp 193–216; (e) De Lucchi, O.; Miotti, U.; Modena, G. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, NY, 1991; Vol. 40, pp 157–405; (f) Russell, G. A.; Mikol, G. J. Acid-catalyzed Rearrangements of Sulfoxides and Amine Oxides. Pummerer and Polonovski Reactions. In *Mechanism of Molecular Migrations*; Thyagarajan, B. S., Ed.; Interscience: New York, NY, 1968; pp 157–207; (g) Oae, S.; Numata, T. The Pummerer and Pummerer-type Reactions. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: New York, NY, 1980; Vol. 5, pp 45–102.
2. Reviews: (a) Moiseenkov, A. M.; Dragan, V. A.; Veselovskii, V. V. *Russ. Chem. Rev.* **1991**, *60*, 643–657; (b) Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353–1377; (c) Prilezhaeva, E. N. *Russ. Chem. Rev.* **2001**, *70*, 897–920; (d) Padwa, A.; Bur, S. K.; Danca, D. M.; Ginn, J. D.; Lynch, S. M. *Synlett* **2002**, 851–862; (e) Wang, C.-C.; Huang, H.-C.; Reitz, D. B. *Org. Prep. Proced. Int.* **2002**, *34*, 271–319; (f) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401–2432; (g) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003–5034.
3. (a) Fujita, J.; Matsuda, H.; Yamamoto, K.; Morii, Y.; Hashimoto, M.; Okunoa, T.; Hashimoto, K. *Tetrahedron* **2004**, *60*, 6829–6851; (b) McCormick, J. E.; McElhinney, R. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2533–2540; (c) Veerapen, N.; Taylor, S. A.; Walsby, C. J.; Pinto, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 227–239; (d) Matsuda, H.; Fujita, J.; Morii, Y.; Hashimoto, M.; Okunoa, T.; Hashimoto, K. *Tetrahedron Lett.* **2003**, *44*, 4089–4093; (e) Gonzalez, F. S.; Mendoza, P. G.; Aparicio, F. J. L. *Carbohydr. Res.* **1988**, *183*, 227–240.
4. Yoshimura, Y.; Yamazaki, Y.; Kawahata, M.; Yamaguchi, K.; Takahataa, H. *Tetrahedron Lett.* **2007**, *48*, 4519–4522.
5. Spry, D. O. *Tetrahedron Lett.* **1972**, *35*, 3717–3720.
6. Renslo, A. R.; Luehr, G. W.; Lam, S.; Westlund, N. E.; Gómez, M.; Hackbarth, C. J.; Patel, D. V.; Gordeeva, M. F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3475–3478.
7. (a) Heuzé, B.; Gasparova, R.; Heras, M.; Masson, S. *Tetrahedron Lett.* **2000**, *41*, 7327–7331; (b) Heras, M.; Gulea, M.; Masson, S. *Chem. Commun.* **2001**, 611–612; (c) Heras, M.; Gulea, M.; Masson, S.; Philouze, C. *Eur. J. Org. Chem.* **2004**, 160–172; (d) Bastin, R.; Albadri, H.; Gaumont, A.-C.; Gulea, M. *Org. Lett.* **2006**, *8*, 1033–1036.
8. See for examples: (a) Hunter, R.; Simon, C. D. *Tetrahedron Lett.* **1986**, *27*, 1385–1386; (b) Hunter, R.; Simon, C. D. *Tetrahedron Lett.* **1988**, *29*, 2257; (c) Praefcke, K.; Weichsel, C. *Liebigs Ann. Chem.* **1979**, *6*, 784–795.
9. Such β,γ-unsaturated thionium ions can be also formed in a so called 'vinylogous Pummerer reaction' involving an alkenyl sulfoxide; see for examples: (a) Kosugi, H.; Uda, H.; Yamagiwa, J. S. *J. Chem. Soc., Chem. Commun.* **1975**, 192–193; (b) Kitchin, J.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1972**, 959–960.
10. (a) Yuasa, H.; Kamata, Y.; Hashimoto, H. *Angew. Chem., Int. Ed.* **1997**, *36*, 868–870; (b) Le Questel, J.-Y.; Mouhous-Riou, N.; Boubia, B.; Samreth, S.; Barberousse, V.; Pérez, S. *Carbohydr. Res.* **1997**, *302*, 53–66; (c) Bozó, É.; Demeter, Á.; Rill, A.; Kuszmann, J. *Tetrahedron: Asymmetry* **2002**, *12*, 3423–3433; (d) Yuasa, H.; Tsuruta, O.; Hashimoto, H. *Tetrahedron Lett.* **2007**, *48*, 7953–7956.
11. See for example in Ref. 1d: (a) Praefcke, K.; Weichsel, C. D. *Tetrahedron Lett.* **1976**, 2229; (b) Johnson, C. R.; McCants, D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1109.
12. *Typical procedure for a selective sulfoxidation* (Method **A**). *Synthesis of* (**2a**): To a stirred solution of thiopyran **1a** (500 mg, 1.61 mmol) in dry CH_2Cl_2 (5 mL) under nitrogen at −78 °C, was added dropwise a solution of mCPBA (1.1 equiv, 437 mg, 1.77 mmol) in CH_2Cl_2 (4 mL). The mixture was stirrsed at −78 °C for 1 h and then extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford sulfoxide **2a** (436 mg, 1.33 mmol, 83% yield) as a mixture of two diastereomers (93/7). Aspect: colorless oil. R_f: 0.14 (AcOEt). IR (neat, cm^{-1}): 2979, 2930, 1384, 1374, 1245, 1053, 975, 777, 578. Major isomer: ^{31}P NMR (162 MHz, $CDCl_3$) δ = 17.2. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.92–5.84 (m, 1H, H^4), 5.71–5.64 (m, 1H, H^5), 4.96–4.79 (m, 2H, 2 × $CHMe_2$), 3,97–3.88 (m, 1H, H^6), 3.35–3.24 (m, 2H, $H^{6'}$ and H^3), 2.41 (s, 3H, SMe), 2.38–2.29 (m, 1H, $H^{3'}$), 1.40 (d, J = 6.4 Hz, 3H, $CHMe_2$), 1.38 (d, J = 6.0 Hz, 6H, $CHMe_2$), 1.35 (d, J = 6.0 Hz, 3H, $CHMe_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 124.1 (d, J = 10.6 Hz, C^4), 116.3 (d, J = 1.2 Hz, C^5), 73.4 (d, J = 6.9 Hz, $CHMe_2$), 72.8 (d, J = 7.6 Hz, $CHMe_2$), 58.4 (d, J = 153.6 Hz, C^2), 44.7 (d, J = 3.8 Hz, C^6), 24,6 (d, J = 1.5 Hz, $CHMe_2$), 24.4 (d, J = 3.3 Hz, $CHMe_2$), 23.9 (d, J = 5.8 Hz, $CHMe_2$), 23.7 (d, J = 7.1 Hz, $CHMe_2$), 23.9 (s, C^3), 13.8 (s, SMe). HRMS calcd for $C_{12}H_{24}O_4PS_2$: 327.0854; found: 327.0854.
13. *Typical procedure for the Pummerer reaction. Synthesis of compounds* (**6b**) *and* (**7b**): To a stirred solution of sulfoxide **2b** (150 mg, 0.423 mmol) in dry THF (1 mL) under nitrogen at 0 °C, was added dropwise TFAA (65 μL, 0.467 mmol). The mixture was stirred at 0 °C for 1 h and then was extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to yield compounds **6b** (61 mg, 0.181 mmol, 43%) and **7b** (88 mg, 0.229 mmol, 54%). *Compound* (**6b**). Aspect: colorless oil. R_f: 0.49 (pentane/AcOEt: 70/30). IR (neat, cm^{-1}): 2978, 2923, 1384, 1373, 1244, 1103, 975, 896. ^{31}P NMR (162 MHz, $CDCl_3$) δ = 17.6. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.84 (d, J = 5.6 Hz, 1H, H^6), 5.21 (m, 1H, C=CHH), 4.90 (m, 1H, C=CHH), 4.90–4.76 (m, 2H, $CHMe_2$), 3.07 (ddt, J = 14.8, 8.0, 1.9 Hz 1H, H^3), 2.87 (dd, J = 14.8, 7.6 Hz, 1H, $H^{3'}$), 2.32 (d, J = 0.5 Hz, 3H, SMe), 1.98 (d, J = 1.0 Hz, 3H, Me), 1.38 (d, J = 6.0 Hz, 3H, $CHMe_2$), 1.37 (d, J = 6.0 Hz, 3H, $CHMe_2$), 1.36 (d, J = 6.4 Hz, 6H, $CHMe_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.9 (d, J = 10.9 Hz, C^4), 128.4 (s, C^5), 115.0 (d, J = 7.2 Hz, C^6), 114.2 (s, C=CH_2), 73.4 (d, J = 7.4 Hz, $CHMe_2$), 72.7 (d, J = 7.7 Hz, $CHMe_2$), 51.2 (d, J = 160.2 Hz, C^2), 38.1 (s, C^3), 24.6 (d, J = 2.2 Hz, $CHMe_2$), 24.4 (d, J = 2.8 Hz, $CHMe_2$), 23.9 (d, J = 5.8 Hz, $CHMe_2$), 23.7 (d, J = 6.4 Hz, $CHMe_2$), 21.1 (s, Me), 13.3 (s, SMe). HRMS calcd for $C_{14}H_{26}O_3PS_2$: 337.1061; found: 337.1062. *Compound* (**7b**). Aspect: yellow solid; mp: 72–74 °C. R_f: 0.22 (pentane/AcOEt: 70/30). IR (neat, cm^{-1}): 3038, 2980, 2926, 1665, 1572, 1544, 1508, 1272, 1251, 1179, 1133, 1086, 983, 962. ^{31}P NMR (162 MHz, $CDCl_3$) δ = 7.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −77.3. ^1H NMR (400 MHz, $CDCl_3$) δ = 9,43 (d, J = 19.6 Hz, 1H, H^3), 7.42 (d, J = 8.0 Hz, 1H, H^6), 6.01 (d, J = 2.4 Hz, 1H, $CHCOCF_3$), 4.86–4.74 (m, 2H, $CHMe_2$), 2.20 (s, 3H, Me), 1.41 (d, J = 6.4 Hz, 6H, $CHMe_2$), 1.37 (d, J = 6.0 Hz, 6H, $CHMe_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 178.0 (q, J = 32.7 Hz, $COCF_3$), 148.3 (d, J = 14.1 Hz, C^4), 138.8 (d, J = 191.2 Hz, C^2), 133.6 (s, C^5), 132.1 (d, J = 7.9 Hz, C^6), 131.7 (d, J = 8.3 Hz, C^3), 117.1 (q, J = 291.9 Hz, CF_3), 101.1 (s, $CHCOCF_3$), 73.4 (d, J = 6.2 Hz, $CHMe_2$), 24.1 (d, J = 3.9 Hz, $CHMe_2$), 23.9 (d, J = 5.1 Hz, $CHMe_2$), 22.2 (s, Me). HRMS calcd for $C_{15}H_{21}F_3O_4$ PS: 385.0850; found: 385.0850.
14. In addition to the classical 1D and 2D NMR experiments (1D: ^{31}P, ^{19}F, ^1H, $^1H\{^{31}P\}$, ^{13}C, DEPT and 2D: COSY, HMQC), HMBC (Heteronuclear Multiple Bond Correlation Experiment) and NOESY experiments were necessary to identify unambigously compound **7b**. HMBC experiment confirmed: (a) the presence of the six-membered ring (correlation of C^2 and C^5 with H^6 and H^3, of C^4 with H^3 and CH_3); (b) the position of the CF_3CO group (correlation of C^3, C^4, C^5, and CO with CH, of CH with H^3). NOESY experiment confirmed the geometry of the CH=C^4 double bond (correlation of CH with CH_3 and not with H^3).
15. *Cleavage of phosphoryl group. Synthesis of compound* (**8**): A solution of **15** (20 mg, 0.052 mmol) and K_2CO_3 (9 mg, 0.065 mmol) in a mixture of CH_3CN

(1 mL) and MeOH (1 mL) was stirred at reflux for 6 h. The mixture was then extracted with CH_2Cl_2, the organic layer was washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to yield compound **8** (8 mg, 0.036 mmol, 69%). Aspect: yellow-orange solid; mp: 76–78 °C. R_f: 0.67 (pentane/AcOEt: 70/30). ^{19}F NMR (376 MHz, $CDCl_3$) $\delta = -77.6$. ^1H NMR (400 MHz, $CDCl_3$) $\delta = 9.09$ (d, $J = 10.4$ Hz, 1H, H^3), 7.52 (ddd, $J = 10.4$, 3.6, 1.2 Hz, 1H, H^2), 7.40–7.37 (m, 1H, H^6), 5.93 (s, 1H, $CHCOCF_3$), 2.22 (d, $J = 1.2$ Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 177.8$ (q, $J = 31.9$ Hz, $COCF_3$), 150.2 (s, C^4), 134.5 (s, C^5), 133.2 (s, C^2), 131.0 (s, C6), 126.3 (s, C^3), 117.4 (q, $J = 292.0$ Hz, CF_3), 99.0 (s, $CHCOCF_3$), 22.5 (s, Me). HRMS calcd for $C_9H_8F_3OS$: 221.0248; found: 221.0258.