Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 4671–4675

Mild generation of *o*-quinodimethanes via fluoride induced 1,4-elimination of α-(*o*-trimethylsilylmethyl)benzylesters: stereoselective synthesis of 19-nor steroids and RU486 precursors

Marc Port[†] and Robert Lett[*]

Unité Mixte CNRS-ROUSSEL UCLAF (UMR 26) 102, route de Noisy, 93235 Romainville, France

Received 23 March 2006; revised 19 April 2006; accepted 26 April 2006
Available online 22 May 2006

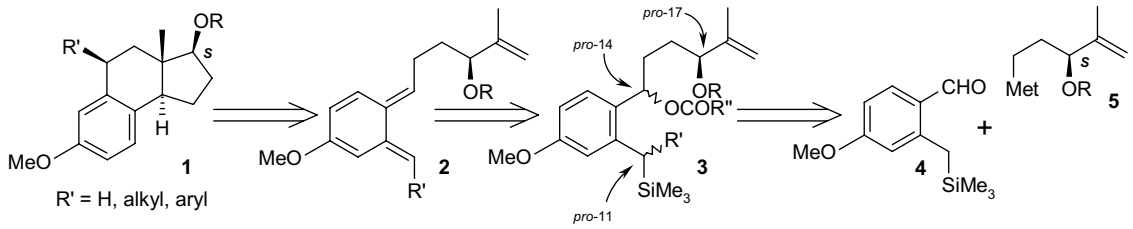
Abstract—19-Nor steroids and RU486 tricyclic synthetic intermediates were stereoselectively prepared by an intramolecular Diels–Alder reaction involving an *o*-quinodimethane possessing a *pro*-17 unique chiral stereocenter, substituted by a protected hydroxyl group. The *o*-quinodimethane was generated in mild conditions by fluoride induced 1,4-elimination of α-(*o*-trimethylsilylmethyl)benzylesters and the present methodology allows a flexible access to α,α′-disubstituted *o*-quinodimethanes, as shown by the 11β-substituted steroid approach. The IMDA diastereoselections reported herein were highly dependent on the nature of the hydroxyl protective group and the diastereoselectivities superior to those observed with the thermolysis of the corresponding benzocyclobutenes.

1. Introduction

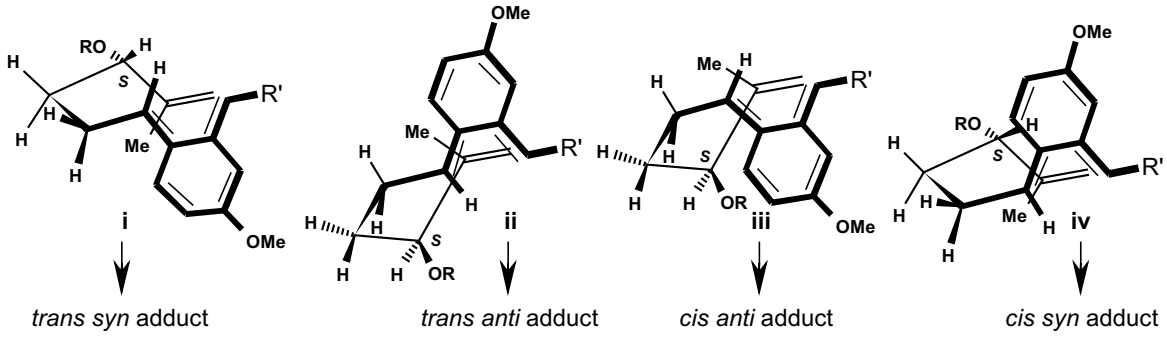
Intramolecular cycloadditions of *o*-quinodimethane intermediates have been extensively studied by many groups in total synthesis, and especially in that of steroids.[1–3] Although different routes for generating in situ, the *o*-quinodimethane intermediate have shown quite a potential, it might be worth trying to simplify the access to its precursor and to make it more flexible with regard to its structure, especially for the preparation of α,α′-disubstituted *o*-quinodimethanes. It might also be useful to generate the *o*-quinodimethane in milder conditions than those required for the thermolysis of benzocyclobutenes or that of cyclic sulfones. Thus, we were particularly interested by the mild conditions (acetonitrile, 50 °C) developed by Saegusa, for fluoride ion induced 1,4-elimination of *o*-(α-trimethylsilylalkyl)benzyltrimethylammonium salts.[4] Moreover, quite remarkably in a synthesis of (*d*,*l*)-11α-hydroxyestrone, Magnus generated the required *o*-xylylene intermediate from the opening of an epoxide, triggered by fluoride cleavage of the C–Si bond in diglyme at 27 °C, to obtain the desired IMDA cycloadduct in 70% yield.[5] Hence, for an asymmetric synthesis of 19-norsteroids and 11β-substituted steroids, we examined another route involving a fluoride anion induced 1,4-elimination with an ester as a leaving group, which might have a greater flexibility for the substitution of the aromatic part of the precursor and for the substitution at the α,α′ positions by an alkyl or an aryl substituent.[6] Thus, also based on the pioneering work of Kametani and Fukumoto,[7] and starting from a precursor **3** for generating an *o*-quinodimethane **2** having a unique chiral stereocenter at *pro*-17, our aim was to see if we might obtain efficiently and highly stereoselectively the desired enantiopure cycloadduct **1** from a precursor such as **3** (Scheme 1). The required absolute configurations of the C_{11}, C_{13}, and C_{14} stereocenters of a steroid might be obtained from a protected hydroxyl group of *S* configuration via transition state **i**, or from the enantiomer *R* via the enantiomeric transition state of **ii**. Hence a precursor, substituted at the *pro*-11 position, should thus afford the 11β-substituted cycloadduct, provided one of the two transition states, **i** or **ii**, is sufficiently favored with the proper configuration of the unique chiral stereocenter (Scheme 2). In this note, we report our results concerning the mild and efficient generation of *o*-quinodimethanes from precursors such as **3**, easily obtained

* Corresponding author at present address: ICMMO, UMR CNRS 8182, bâtiment 410, Université de Paris-Sud, 91405 Orsay Cedex, France. Tel.: +33 1 69 15 63 03; fax: +33 1 69 15 46 79; e-mail: robert.lett@icmo.u-psud.fr
† Present address: Guerbet Research, BP 57400, 95943 Roissy CDG Cedex, France.

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.129



Scheme 1.

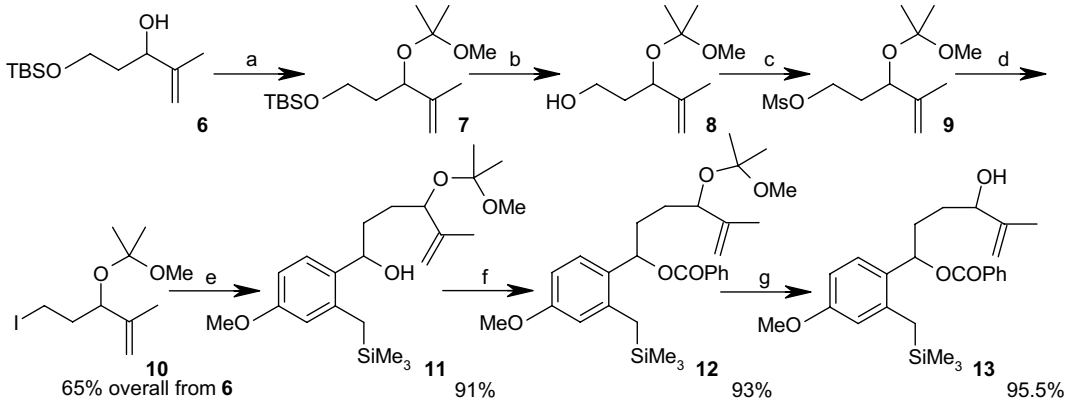


Scheme 2.

from **4** and **5** (Scheme 1), and also the diastereoselectivities obtained in such cycloaddition conditions with a racemic precursor in preliminary studies.[6]

2. Convergent synthesis of the *o*-quinodimethane precursors (Scheme 3)

In order to also further examine the influence of the nature of the hydroxyl protective group on the stereoselectivity of the intramolecular cycloaddition,[7] a convergent synthesis leading to the key-intermediate **13** was achieved, involving the protection of the *pro*-17 hydroxyl as a mixed ketal with 2-methoxypropene for the whole sequence **6** (prepared in three steps from 4-penten-1-ol, 69% overall yield) to **12**. Iodide **10** was thus obtained after flash chromatography in 65% overall yield from **6**, with no intermediate purification. Reaction of the lithio derivative prepared from iodide **10**, via halogen–lithium exchange,[8] with aldehyde **4**[5,9] (0.95 equiv) afforded intermediate **11** in 91% yield, as a 60/40 mixture of two diastereoisomers. Further benzoylation (93%) and hydrolysis in mild acidic conditions gave **13** as a 60/40 mixture of diastereoisomers which were not separated (95.5%). It is worth pointing out that the choice of that *pro*-17 hydroxyl protective group, in addition to the advantages of its simplicity and of not introducing a supplementary stereogenic center, gave far better results than a THP ether, allowing in the hydrolysis step to completely avoid the formation of a five-membered cyclic ether which was always formed with the THP ether in different acidic conditions.[6]



Scheme 3. Reagents and conditions: (a) $POCl_3$ (1 mol %), 2-methoxypropene (1.5 equiv), CH_2Cl_2, rt; (b) TBAF 1 M (1.1 equiv), THF, rt; (c) MsCl (1.13 equiv), NEt_3 (1.2 equiv), *i*-$PrNEt_2$ (0.25 equiv), CH_2Cl_2, 0 °C→rt; (d) NaI (5 equiv), *i*-$PrNEt_2$ (0.2 equiv), acetone, rt; (e) **10**, *t*-BuLi (1.9 equiv), Et_2O–pentane, −78 °C, 3 min, then **4** (0.95 equiv), −78 °C→rt; (f) PhCOCl (2 equiv), DMAP cat., pyridine, rt and (g) PPTS (0.1 equiv), EtOH, rt.

3. In situ *o*-quinodimethane formation and intramolecular cycloaddition

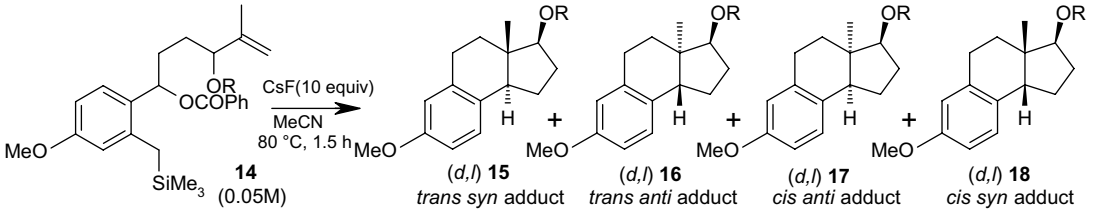
Quite surprisingly, an ester as a leaving group was never really examined before this work.[6] We only found an isolated previous example of fluoride induced elimination on *o*-(acetoxymethyl)benzyltrimethylsilane[10] and another one on 2-(acetoxymethyl)-3-(triisopropylsilylmethyl)-benzofuran[11] when this study was initiated. With derivatives of **3** (R = MEM, R′ = H), we first examined different conditions in order to get an efficient in situ generation of the *o*-quinodimethane intermediate and IMDA cycloadducts formation. Noteworthy, no significant difference in reactivity was observed for the two diastereoisomers, which are epimeric at *pro*-14, as shown by following their conversion, consistently with earlier results of Saegusa in a parent methodology.[4] In similar anhydrous conditions (CsF (10 equiv), MeCN, 80 °C), for **3** (R = MEM, R′ = H, 0.05 M), the global yields of cycloadducts were quite comparable (67.5–71%) with the acetate, benzoate, and *p*-methoxybenzoate, but significantly lower with the *p*-nitrobenzoate (30%). No significant difference of IMDA stereoselectivity was observed for all those esters.

Concerning the source of the fluoride, TBAF/THF was not satisfactory, leading to protodesilylation products, due to the difficulty to get anhydrous TBAF.[12] Anhydrous CsF, which is easy to obtain (200 °C, 0.8 mmHg) gave better results than KF in MeCN. However, KF or CsF (2 equiv) gave comparable yields of cycloadducts in sulfolane (89.5% and 92%). The stannate [*n*-Bu_4N^+, $Ph_3SnF_2^-$],[13] which is soluble in many organic solvents and not hygroscopic, gave good yields of cycloadducts from **3** (R = MEM, R′ = H, R″ = Ph, 0.05 M) in MeCN (89%), DMF (97.5%), and DMPU (93.5%), at 80 °C. However conversion was much slower in MeCN with the stannate as a source of fluoride, than with CsF. Concentration of the precursor **3** (R = MEM, R′ = H, R″ = Me or Ph) was always found to be quite optimal at 0.05 M to obtain good yields of the cycloadducts and a higher concentration (0.5 M) led to a significantly lower yield (R″ = Me, 42.5%), due to intermolecular reactions and dimerization.

With **3** (R = MEM, R′ = H, R″ = Me or Ph, 0.05 M) and CsF (2 equiv), at 80 °C, polar solvents like DMF, sulfolane, and DMPU gave faster conversions than MeCN and good yields of cycloadducts. With respect to MeCN, at 80 °C, other solvents like THF, DME or diglyme gave slower reactions and lower yields. On the other hand, **3** (R = MEM, R′ = H, R″ = Ph) gave with CsF (2 equiv) in DMSO, at 80 °C, a much faster reaction, but those reaction conditions led to much intermolecular reactions at 0.05 M and to a lower yield of cycloadducts (44%). No solvent effect or influence of the source of the fluoride was observed on IMDA stereoselectivity, at the same temperature.

Benzocyclobutenes were not observed and shown not to be intermediates. It is worth to point out that, for the TBS ether $\mathbf{14_K}$, the yield of cycloadducts was significantly improved with the stannate [*n*-Bu_4N^+, $Ph_2SnF_2^-$] with respect to CsF (Table 1). Also noteworthy, alcohol **13** led to much protodesilylation (21%) and the corresponding lithium alkoxide here was unsatisfactory.[6] With $\mathbf{14_B}$ (0.05 M, toluene, 80 °C, 23 h), potassium trimethylsilanolate (1.2 equiv) was found to yield only 15.5% of cycloadducts and the major product (68%) resulted from a Brook rearrangement of the *pro*-11 alcoholate

Table 1. Yields and diastereoselectivity of the Diels–Alder reaction from the *o*-quinodimethane generated in situ



R = H	**13**	20.5%	$\mathbf{15_A}$	36%	$\mathbf{16_A}$	55%	$\mathbf{17_A}$	3%	$\mathbf{18_A}$	6%
R = MEM	$\mathbf{14_B}$	82%	$\mathbf{15_B}$	58%	$\mathbf{16_B}$	29%	$\mathbf{17_B}$	2%	$\mathbf{18_B}$	11%
R = MOM	$\mathbf{14_C}$	63.5%	$\mathbf{15_C}$	58%	$\mathbf{16_C}$	29%	$\mathbf{17_C}$	2%	$\mathbf{18_C}$	11%
R = DMPM	$\mathbf{14_D}$	58%	$\mathbf{15_D}$	63%	$\mathbf{16_D}$	25%		$\mathbf{17_D} + \mathbf{18_D}$ 12%[a]		
R = THP	$\mathbf{14_E}$	65%	$\mathbf{15_E}$	55%	$\mathbf{16_E}$	33%	$\mathbf{17_E}$	2%	$\mathbf{18_E}$	9%
R = CMe_2(OMe)	$\mathbf{14_F}$	96%	$\mathbf{15_F}$	46%	$\mathbf{16_F}$	45%	$\mathbf{17_F}$	2%	$\mathbf{18_F}$	7%
R = $COCF_3$	$\mathbf{14_G}$	80%	$\mathbf{15_G}$	55%	$\mathbf{16_G}$	23%	$\mathbf{17_G}$	4%	$\mathbf{18_G}$	18%
R = *p*-NO_2-C_6H_4-CO	$\mathbf{14_H}$	23.5%	$\mathbf{15_H}$	48%	$\mathbf{16_H}$	32%	$\mathbf{17_H}$	7%	$\mathbf{18_H}$	13%
R = *p*-MeO-C_6H_4-CO	$\mathbf{14_I}$	68.5%	$\mathbf{15_I}$	41%	$\mathbf{16_I}$	40%	$\mathbf{17_I}$	8%	$\mathbf{18_I}$	11%
R = Piv	$\mathbf{14_J}$	70.5%	$\mathbf{15_J}$	37%	$\mathbf{16_J}$	48%	$\mathbf{17_J}$	4%	$\mathbf{18_J}$	10%
R = TBS	$\mathbf{14_K}$	69%	$\mathbf{15_K}$	26%	$\mathbf{16_K}$	64%	$\mathbf{17_K}$	4%	$\mathbf{18_K}$	5%
		80.5%[b]		27.5%		62%		4.5%		5.5%

[a] Deprotection of the DMPM (3,4-dimethoxybenzyl) protective group was here not achieved, and the ratio of the two *cis*-fused could not be determined.

[b] $\mathbf{14_K}$ (0.05 M), [*n*-Bu_4N^+, $Ph_3SnF_2^-$] (2 equiv), anhyd DMF, 80 °C, 45 h.

formed in situ. On the other hand, no *o*-quinodimethane was formed from **3** (R = MEM, R′ = H, R″ = Me) in the conditions reported by Mann (CCl_4, SiO_2, 80 °C).[14]

4. *Pro*-17 hydroxyl protective group influence on IMDA diastereoselectivity (Table 1)

Using standard conditions, the *pro*-17 hydroxyl was protected very efficiently by different groups. For each IMDA, the stereoselectivities were determined on $\mathbf{15_A}$, $\mathbf{16_A}$, $\mathbf{17_A}$, and $\mathbf{18_A}$, after cleavage of the hydroxyl protective group on the crude product, by ^{1}H NMR integration of the distinct angular methyl group for each diastereomer (200 MHz, $CDCl_3$) and by HPLC (Lichrosorb Si 60 μm; eluent: 11:89:0.2 EtOAc/hexane/AcOH; flow rate: 2 mL/min; t_R (min): $\mathbf{16_A}$, 13.66; $\mathbf{18_A}$, 14.75; $\mathbf{17_A}$, 16.38; $\mathbf{15_A}$, 18.21). Structures of the cycloadducts were unambiguously assigned by identification of $\mathbf{15_A}$ with a reference sample provided by Roussel Uclaf, and by chemical filiation.[15] The results are given in Table 1 and they were shown to be kinetic results, since we checked that diastereoselectivity was the same at different conversions of the precursor and that isolated cycloadducts remained unchanged in reaction conditions.[6]

As already observed in the thermolysis of benzocyclobutenes by Kametani and Fukumoto,[7] and now in the present work,[6,15] IMDA diastereoselection is highly dependent on the nature of the protective group of the *pro*-17 hydroxyl as a unique chiral stereocenter of the generated *o*-quinodimethane. With respect to the results obtained by thermolysis at 180 °C of the corresponding benzocyclobutenes, diastereoselectivity is slightly improved by in situ generation of the *o*-quinodimethane at 80 °C from precursors such as **3**.[6,15] From each precursor, the *trans*-hydrindanes are the major cycloadducts and the configuration of the major *trans*-hydrindane cycloadduct can be changed depending on the *pro*-17 hydroxyl protective group, as already observed for silyl ethers by Kametani and Fukumoto,[7] but also with other protective groups such as here the pivalate $\mathbf{14_J}$ or the *t*-butyl ether.[9] The formation of the *cis anti* adduct **17** can be expected as a minor cycloadduct, and rationalized to some extent by considering the strong steric interactions of the OR group with the *o*-quinodimethane subunit involved in transition state **iii** (Scheme 2). With respect to the *trans syn* and *trans anti* cycloadducts, the rationalization of the nature of the major isomer appears to be quite difficult and these results, with those later obtained,[9] clearly show that the IMDA stereoselectivity is at present difficult to understand.

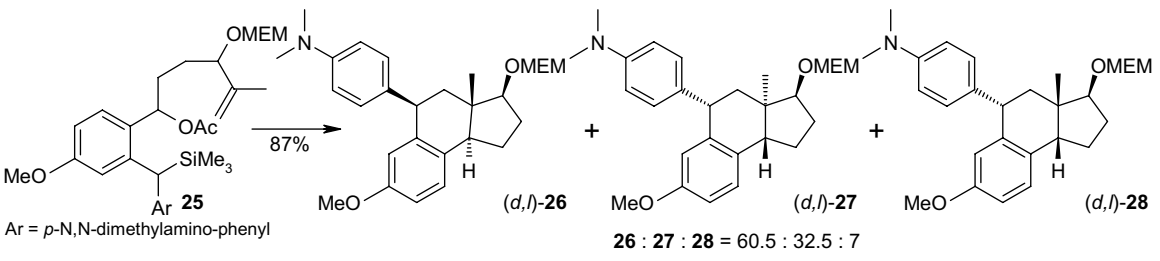
5. Temperature effects on diastereoselectivity

As anticipated for an IMDA, there was only a slight effect of the temperature on diastereoselectivity and the conversions were too slow at 25 °C to be of preparative interest, although the stereoselectivity was then improved (Supplementary data).[6]

6. α,α′-disubstituted *o*-quinodimethanes: a synthetic approach of RU486 (mifepristone) (Scheme 4)

In preliminary studies concerning a new synthetic approach of RU486 or more generally of 11β-substituted steroids, we first examined on racemic intermediates, prepared from (*d*,*l*)-**6**, if we might extend our methodology to the preparation of α,α′-disubstituted *o*-quinodimethanes and achieve the corresponding IMDA to afford stereoselectively the desired synthon **26**. Thus, the precursor **25** was obtained as a mixture of diastereoisomers, starting from *p*-*N*,*N*-dimethylamino-benzaldehyde.[6] Further reaction of **25** (0.05 M) with CsF (12 equiv) in CH_3CN, at 80 °C for 2 h gave only 56% of the cycloadducts **26**, **27**, **28** in a ratio 61.5:31:7.5, and 37% of *o*,*o*′-quinodimethane dimers were isolated. Best results were obtained by the reaction of **25** (0.05 M) with [*n*-Bu_4N^+, $Ph_3SnF_2^-$] in anhydrous DMF, at 80 °C for 48 h, which afforded in 87% yield the cycloadducts **26**, **27**, and **28** as a 60.5:32.5:7 mixture, and no dimers were formed in those conditions. Either with the stannate or with CsF, no difference of reactivity between the diastereoisomers of **25** was noticed and no traces of the fourth possible cycloadduct were observed. The structures of the cycloadducts **26**, **27**, and **28** were assigned unambiguously by ^{1}H and ^{13}C NMR.[6]

As a conclusion, the present methodology is quite simple and flexible for the in situ generation of *o*-quinodimethanes from precursors such as **3**. Quite remarkably, the relative rates for the formation of the intermediate *o*-quinodimethane and for the *intramolecular* cycloaddition remain compatible from 25 to 180 °C to afford good yields of the cycloadducts, with no dimerization or intermolecular reactions in the appropriate reaction conditions reported herein. Precursors such as **3** were also shown in *intermolecular* Diels–Alder reactions to give re-



Scheme 4. Reagents and conditions: [*n*-Bu_4N^+, $Ph_3SnF_2^-$] (2 equiv), anhyd DMF, 80 °C, 48 h.

sults quite comparable to those obtained by the methodology developed by Ito and Saegusa,[4a,c] with the same dienophiles.[9] During the completion of this work and after it, some related results were also reported for fluoride-induced elimination of an ester[14,16] or a sulfone.[17]

The present method involving *o*-quinodimethane precursors such as **3** was also applied to the asymmetric synthesis of 19-nor steroids such as enantiopure trenbolone acetate, starting from enantiopure (*S*)-**6**.[6] As shown also by our synthetic approach of RU486 (mifepristone) from **3** (R = MEM, R′ = *p*-NMe_2-C_6H_4-, R″ = Me), the methodology described herein gives a good access to α,α′-disubstituted *o*-quinodimethanes which are difficult to synthetize by other methods.[1–4]

Acknowledgments

We thank the staff of the Analytical Department of the Roussel Uclaf Research Center at Romainville and also Roussel Uclaf and the CNRS for a Ph.D. Grant to M. Port, the Direction des Recherches Chimiques of Roussel Uclaf for support of this work.

Supplementary data

Temperature effects (25–180 °C) on IMDA yield and diastereoselectivity are given for $\mathbf{14_B}$ (R = MEM, R″ = Ph) and $\mathbf{14_K}$ (R = TBS, R″ = Ph). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.129.

References and notes

1. (a) Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 3378–3379; (b) Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3–16; (c) Nemoto, H.; Fukumoto, K. *Tetrahedron* **1998**, *54*, 5425–5464.
2. (a) Oppolzer, W. *Synthesis* **1978**, 793–802; (b) Oppolzer, W. *Heterocycles* **1980**, 1615–1630.
3. Michellys, P.-Y.; Pellissier, H.; Santelli, M. *Org. Prep. Proc. Int.* **1996**, *28*, 545–608.
4. (a) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 863–865; (b) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1981**, *103*, 476–477; (c) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609–7622.
5. Djuric, S.; Sarkar, T.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 6885–6886.
6. Port, M. Ph.D. Thesis, Paris VI University, 1995.
7. (a) Kametani, T.; Matsumoto, H.; Honda, T.; Fukumoto, K. *Tetrahedron Lett.* **1980**, 4847–4848; (b) Kametani, T.; Matsumoto, H.; Honda, T.; Nagai, M.; Fukumoto, K. *Tetrahedron* **1981**, *37*, 2555–2560; (c) Nemoto, H.; Matsuhashi, N.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1991**, 705–706; (d) Nemoto, H.; Matsuhashi, N.; Satoh, A.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 495–498.
8. (a) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210–7211; (b) Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847–853.
9. Delpech, B.; Lett, R., unpublished results.
10. Askari, S.; Lee, S.; Perkins, R. R.; Scheffer, J. R. *Canad. J. Chem.* **1985**, *63*, 3526–3529.
11. Bedford, S. B.; Begley, M. J.; Cornwall, P.; Knight, D. W. *Synlett* **1991**, 627–629.
12. (a) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216–3219; (b) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429–452; Clark, J. H.; Smith, D. K. *Tetrahedron Lett.* **1985**, *26*, 2233–2236.
13. (a) Gingras, M. *Tetrahedron Lett.* **1991**, *50*, 7381–7384; (b) Sau, A. C.; Carpino, L. A.; Holmes, R. R. *J. Organomet. Chem.* **1980**, *197*, 181–197.
14. Beard, A. R.; Hazell, S. J.; Mann, J.; Palmer, C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1235–1238.
15. Port, M.; Lett, R. *Tetrahedron Lett.*, accompanying paper, doi: 10.1016/j.tetlet.2006.04.128.
16. (a) Bedford, S. B.; Begley, M. J.; Cornwall, P.; Foreman, J. P.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2827–2832; (b) Leung, M.; Trahanovsky, W. S. *J. Am. Chem. Soc.* **1995**, *117*, 841–851; (c) Fleming, I.; Morgan, I. T.; Sarkar, A. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2749–2763.
17. (a) Lenihan, B. D.; Shechter, H. *Tetrahedron Lett.* **1994**, *35*, 7505–7508; (b) Lenihan, B. D.; Shechter, H. *J. Org. Chem.* **1998**, *63*, 2072–2085; (c) Lenihan, B. D.; Shechter, H. *J. Org. Chem.* **1998**, *63*, 2086–2093.