Pergamon

Tetrahedron Letters 41 (2000) 7225–7230

TETRAHEDRON LETTERS

Concise and stereocontrolled synthesis of polysubstituted tetrahydropyrans

István E. Markó* and Bernard Leroy

Université Catholique de Louvain, Département de Chimie, Bâtiment Lavoisier, Place Louis Pasteur 1, B-1348, Louvain-la-Neuve, Belgium

Received 14 June 2000; accepted 12 July 2000

Abstract

A range of polysubstituted tetrahydropyrans can be readily assembled by a novel methodology involving a metallo-ene reaction coupled with an intramolecular Sakurai cyclisation (IMSC)

Keywords: allylation; cyclisation; Sakurai reactions; ene reactions; carbamates.

Numerous biologically active natural products contain, embedded in their complex architectural framework, a polysubstituted tetrahydropyran subunit. The widespread occurrence of tetrahydropyrans, coupled with their key role as pharmacophores, has stimulated the development of a plethora of elegant methodologies for their stereocontrolled assembly.[1] As part of a synthetic programme aimed at the efficient preparation of tetrahydropyran-containing natural products, we required a rapid, stereocontrolled and stereodivergent route to the three diastereomeric diols **1**–**3** (Fig. 1).

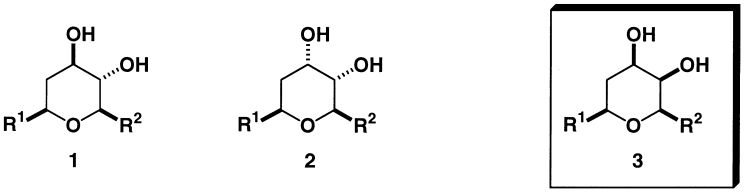


Figure 1.

In a previous communication, we have reported on a novel, three-component methodology, that provided us with an easy access to isomerically pure tetrahydropyrans **1** and **2**.[2] This

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01179-5

protocol involves an initial, abnormal, ene reaction between allylsilane **4** and an aldehyde, affording silylenol ether **5** solely as the (*E*)-geometric isomer.[3] Subsequent intramolecular cyclisation via oxocarbenium ion **7** generated diastereomerically pure *exo*-methylene tetrahydropyran **6**. The 2,3-*anti*, 2,6-*syn*-stereochemistry derived from the preferred pseudo-equatorial arrangement of the substituents in intermediate **7**. Oxidative cleavage of the exocyclic C–C double bond, followed by stereoselective reduction with the appropriate hydrides, ultimately provided diols **1** and **2** in high overall yields (Fig. 2).[4]

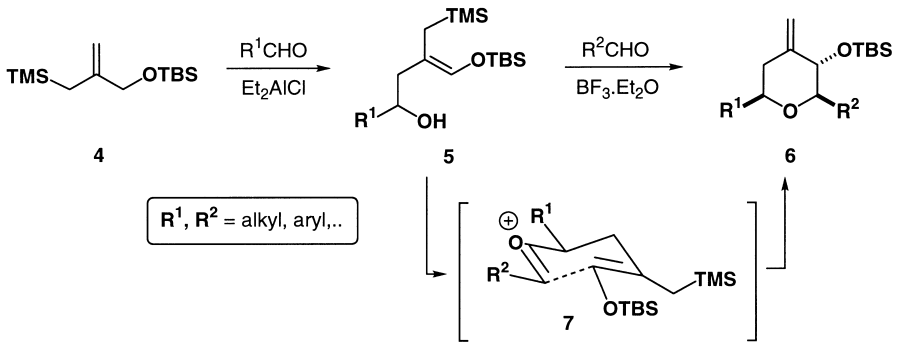


Figure 2.

Unfortunately, the subsequent transformation of **1** or **2** into isomer **3** proved to be lengthy and cumbersome. We envisioned that a rapid access to the desired tetrahydropyrans **3** could be realised starting from the (*Z*)-isomer of enol ether **5**. In this article, we wish to report our preliminary results on the successful implementation of this strategy.

With the desired (*Z*)-silylenol ethers being unattainable by the previous methodology, we selected the corresponding carbamate derivatives **10**. These compounds should be readily available by the the elegant allyl-metallation protocol reported by Hoppe (Fig. 3).[5]

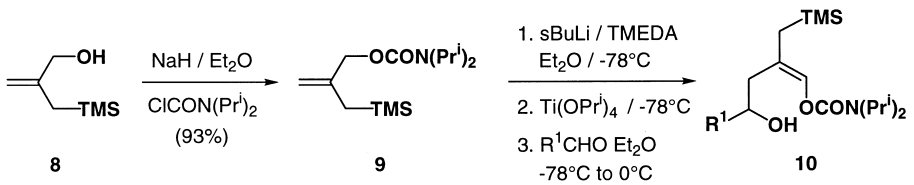
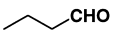
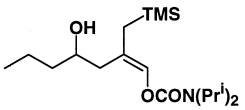
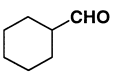
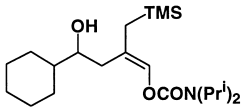
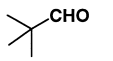
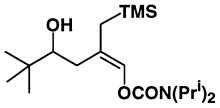
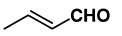
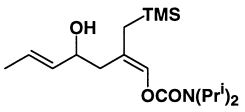
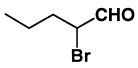
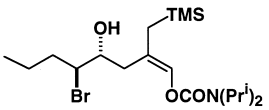
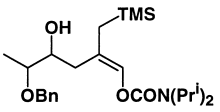


Figure 3.

Thus, allyl alcohol **8** was transformed into carbamate **9** by condensation with diisopropyl carbamoyl chloride in excellent yield. Metallation of **9** proved unexpectedly difficult and proceeded only under the conditions described in Fig. 3. Gratifyingly, addition of $Ti(OPr^i)_4$ to a solution of the in situ generated allyllithium reagent, followed by an aldehyde led in high yield to the desired (*Z*)-enolcarbamate **10** as a single geometric isomer.[6] A collection of representative examples is displayed in Table 1.

Primary, secondary and tertiary aliphatic aldehydes reacted smoothly (Entries 1–3) and so did unsaturated aldehydes (Entry 4). Whilst in some cases, the allylation reaction displayed complete diastereoselectivity (Entry 5), in other cases, it proceeded with modest stereocontrol (Entry 6).

Table 1
Metallo-ene reaction of allylcarbamate **9**

Entry	R^1CHO	Product	Yield[(a)]	d.e.[(b)]
1			71%	-
2			70%	-
3			66%	-
4			56%	-
5			77%	>99%
6			63%	23%

[(a)] All yields refer to pure, isolated products. All new compounds were fully characterised by spectroscopic and elemental analysis. [(b)] The d.e.'s were measured by ^1H NMR spectroscopy.

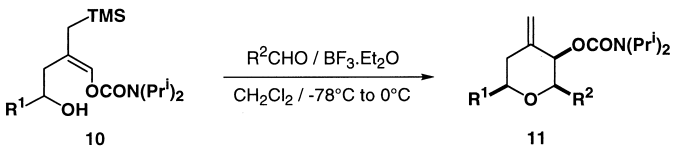
With ready access to the desired (*Z*)-enolcarbamates at hand, we next turned our attention to the crucial intramolecular Sakurai cyclisation (IMSC).[7] To the best of our knowledge, the IMSC reactions of substrates such as **10** have never been reported before.

After some experimentation, we were delighted to find that, in the presence of $BF_3{\cdot}Et_2O$, a range of enol carbamates smoothly underwent IMSC condensation with a variety of aldehydes, affording the corresponding *exo*-methylene tetrahydropyrans **11** in excellent yields. Even more pleasing was the obtention, in all cases, of a single diastereoisomer possessing the expected C_3-axial alkoxy-substituent (Table 2).

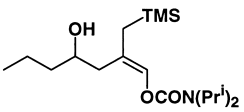
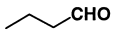
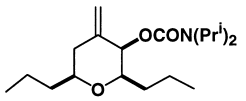
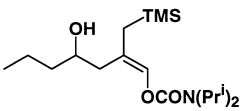
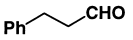
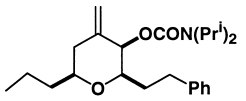
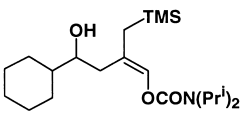
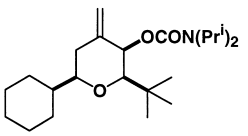
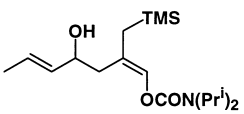
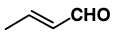
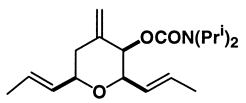
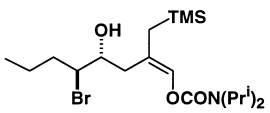
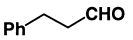
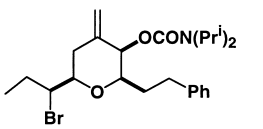
The presence of the C_3-substituent in the axial position was clearly revealed by comparing the values of the coupling constants between the previously prepared, equatorially disposed, pyran derivative **13** with the newly obtained axial isomer **12** (Fig. 4).[8]

Subsequent transformations of **12** into diols such as **3** proceeded smoothly. Ozonolysis of the *exo*-methylene double bond afforded ketone **14** which was reduced by L-Selectride®, providing the *syn*-hydroxycarbamate **15** as a single diastereoisomer. Deprotection of the carbamate function was accomplished smoothly using $LiAlH_4$.[9] It is interesting to note that these two separate operations could be efficiently combined in a single step. Indeed, treatment of ketocarbamate **14** with $LiAlH_4$ not only resulted in the stereoselective reduction of the ketone function but also in the unravelling of the protecting group, affording directly *syn*-diol **16** in 98% overall yield (Fig. 5).

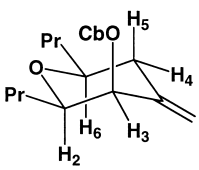
Table 2
Intramolecular Sakurai cyclisation of enol carbamates



10 11

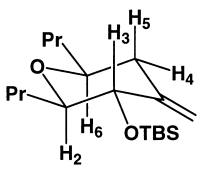
Entry	Substrate	R^2CHO	Product	Yield[a]
1				91%
2				81%
3				78%
4				88%
5				85%

(a) Yields refer to pure, isolated products. The structures of the new compounds were fully established by spectroscopic techniques and elemental analyses.



12

J(H$_2$,H$_3$) ~ 0 Hz
J(H$_6$,H$_5$) = 13.2 Hz
J(H$_6$,H$_4$) = 3.5 Hz



13

J(H$_2$,H$_3$) = 9.0 Hz
J(H$_6$,H$_5$) = 13.2 Hz
J(H$_6$,H$_4$) = 2.0 Hz

Figure 4.

In summary, we have developed an efficient and stereocontrolled access to a variety of polysubstituted tetrahydropyrans by a unique combination of the Hoppe allylmetallation of the novel carbamate derivative **9** with an intramolecular Sakurai cyclisation.[10] The tetrahydropyran derivatives **11**, obtained by this methodology, are stereocomplementary to those prepared earlier according to our previously reported ene-IMSC protocol.

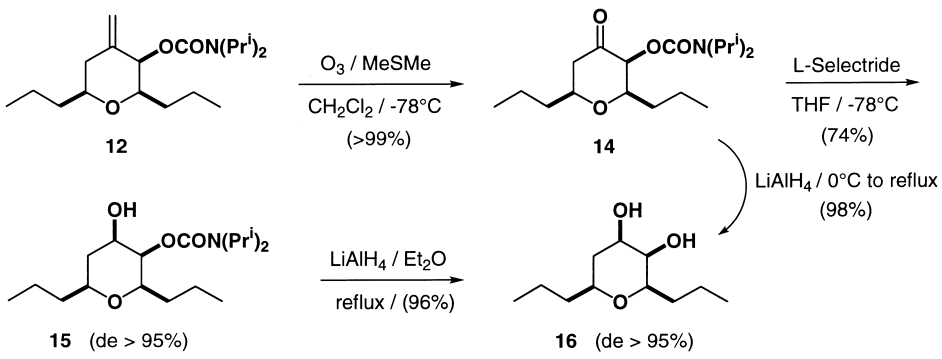


Figure 5.

Acknowledgements

Financial support of this work by the Université catholique de Louvain, the Actions de Recherche Concertées (convention 96/01-197), the Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture (FRIA) and the Fonds de la Recherche Fondamentale Collective (dossier no 2.4571.98) is gratefully acknowledged. I.E.M. is thankful to Merck for its continuous support and for receiving the Merck Young Investigator Award.

References

1. For excellent reviews, see: (a) Perron, F.; Albizati, K. M. *Chem. Rev.* **1989**, *89*, 1617. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
2. (a) Markó, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595. (b) Markó, I. E.; Bayston, D. J. *Tetrahedron* **1994**, *50*, 7141. (c) Markó, I. E.; Bayston, D. J. *Synthesis* **1996**, 297. (d) Feneau-Dupont, J.; Declercq, J. P.; Bayston, D. J.; Markó, I. E. *Bull. Soc. Chim. Belg.* **1997**, *106*, 173.
3. For related ene-reactions of allylsilanes, see: (a) Mikami, K.; Loh, T.-P.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 6737. (b) Mikami, K.; Shimizu, M.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 2952. For a study on the influence of an allylic alkoxy-substituent on ene-reactions, see: (c) Tanino, K.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* **1990**, *31*, 2165. (d) Shoda, H.; Nakamura, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 6281.
4. For synthetic applications, see: Markó, I. E.; Plancher, J.-M. *Tetrahedron Lett.* **1999**, *40*, 5259, and references cited therein.
5. (a) Hoppe, D.; Krämer, T.; Schwark, J.-R.; Zschage, O. *Pure Appl. Chem.* **1990**, *62*, 1999. (b) Zschage, O.; Schwark, J.-R.; Krämer, T.; Hoppe, D. *Tetrahedron* **1992**, *48*, 8377. (c) Berque, I.; Le Ménez, P.; Razon, P.; Mahuteau, J.; Férézou, J.-P.; Pancrazi, A.; Ardisson, J.; Brion, J.-D. *J. Org. Chem.* **1999**, *64*, 373.
6. The geometry of the enolcarbamate was established by NMR spectroscopy and corroborates the results published earlier by Hoppe (Ref. 5a, b).
7. For selected examples of IMSC reactions, see: (a) Markó, I. E.; Chellé, F. *Tetrahedron Lett.* **1997**, *38*, 2895. (b) Markó, I. E.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899. (c) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375, and references cited therein.
8. The sole formation of the axial isomer reinforce our proposed chair-like transition state **7** for the IMSC cyclisation. It is also interesting to note that in these IMSC reactions, no competing [3,3]-sigmatropic rearrangements, that would lead to equatorial products, took place. (a) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426. (b) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776.

9. It is noteworthy that attempted deprotection of pyran derivative **12** could not be accomplished. In this case, recourse to a modified carbamate function proved mandatory (Leroy, B.; Markó, I. E., unpublished results). For the synthesis of the protecting group, see: Derwing, C.; Hoppe, D. *Synthesis* **1996**, 149.
10. Typical experimental procedure. Preparation of **12**: To a solution of TMEDA (1.114 ml, 7.38 mmol) in dry diethyl ether (15 ml) at –78°C was added *sec*-BuLi (1.3 M in hexanes, 5.677 ml, 7.38 mmol) and the mixture was stirred at –78°C for 30 min. A solution of allylsilane **9** (1 g, 3.69 mmol) in diethyl ether (15 ml) was then slowly added, and the mixture stirred at –78°C for 30 min. Titanium tetraisopropoxide (3.268 ml, 11.07 mmol) was then quickly added, and the mixture stirred at –78°C for 30 min. A solution of butyraldehyde (399 mg, 5.53 mmol) in diethyl ether (15 ml) was then quickly added at –78°C and the temperature was allowed to warm to 0°C. After stirring for 10 min, the reaction mixture was poured onto 1N HCl (40 ml) and extracted with diethyl ether. The organic layer was washed with saturated $NaHCO_3$ (40 ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column-chromatography (silica gel, petroleum ether:ethyl acetate, 8:1) to give the alcohol **10** as a colourless oil (901 mg, 71%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.79 (s, 1H), 3.75–3.94 (m, 3H), 2.36 (dd, J = 13.2 Hz, 9.3 Hz, 1H), 2.09 (dd, J = 13.4 Hz, 3.8 Hz, 1H), 1.78 (bs, 1H), 1.01–1.51 (m, 4H), 1.23 (d, J = 6.5 Hz, 12H), 0.92 (t, J = 6.1 Hz, 3H), 0.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.94, 132.61, 119.00, 69.92, 46.92, 40.21, 39.31, 21.72, 21.60, 19.58, 14.82, –0.49. IR (film) 3474, 2957, 1700 cm^{-1}. MS (EI) m/z 343 (7%, M$^+$). Anal. calcd for $C_{18}H_{37}NO_3Si$: C, 62.95%; H, 10.89%; N, 4.07%; found: C, 62.93%; H, 10.85%; N, 4.08%. To a solution of alcohol **10** (855 mg, 2.49 mmol) and butyraldehyde (198 mg, 2.74 mmol) in dry CH_2Cl_2 (25 ml) at –78°C was added slowly $BF_3{\cdot}OEt_2$ (338 µl, 2.74 mmol). The temperature was allowed to warm to 0°C over 3 h. The reaction mixture was poured onto saturated $NaHCO_3$ (25 ml) and the aqueous layer was extracted with CH_2Cl_2 (2×25 ml). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column-chromatography (silica gel, petroleum ether:ethyl acetate, 25:1) to give the tetrahydropyran **12** as a colourless oil (737 mg, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.08 (bs, 2H), 4.89 (t, J = 1.6 Hz, 1H), 3.90–4.23 (m, 1H), 3.59–3.72 (m, 1H), 3.34 (ddd, J = 8.2 Hz, 4.5 Hz, 1.4 Hz, 1H), 3.24–3.32 (m, 1H), 2.18 (tt, J = 13.2 Hz, 1.6 Hz, 1H), 2.11 (dd, J = 13.4 Hz, 3.5 Hz, 1H), 1.38–1.66 (m, 8H), 1.19 (d, J = 6.8 Hz, 12H), 0.91 (t, J = 7.1 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.20, 143.23, 113.20, 79.99, 78.43, 74.12, 46.10 (b), 38.42, 37.52, 33.73, 21.20 (b), 18.89, 18.72, 14.03. IR (film) 2960, 1693 cm^{-1}. MS (EI) m/z 325 (12%, M$^+$). Anal. calcd for $C_{19}H_{35}NO_3$: C, 70.00%; H, 10.81%; N, 4.36%; found: C, 70.11%; H, 10.84%; N, 4.30%.