[12] M. Isobe, F. Fukuda, T. Nishikawa, P. Chabert, T. Kawai, T. Goto, *Tetrahedron Lett.* **1990**, *31*, 3327–3330.

[13] a) N. Yamamoto, M. Isobe, *Chem. Lett.* **1994**, 2299–2302; b) T. Nishikawa, N. Ohyabu, N. Yamamoto, M. Isobe, *Tetrahedron* **1999**, *55*, 4325–4340.

[14] M. Isobe, N. Yamamoto, T. Nishikawa in *Levoglucosenone and Levoglucosans, Chemistry and Applications* (Ed.: Z. J. Witczak), ATL Press, **1994**, pp. 99–118.

[15] T. Nishikawa, M. Asai, N. Ohyabu, M. Isobe, *J. Org. Chem.* **1998**, *63*, 188–192.

[16] H. W. Pauls, B. Fraser-Reid, *Carbohydr. Res.* **1986**, *150*, 111–119.

[17] The original conditions described by Luche and Gamal using MeOH as a solvent gave a low yield of **4** and recovered starting material; J. L. Luche, A. L. Gamal, *J. Am. Chem. Soc.* **1979**, *101*, 5848. On the other hand, the reduction with the solvent system ($EtOH-CH_2Cl_2$) reported by Danishefsky et al. gave our desired product **4** in better yield and with higher selectivity; S. J. Danishefsky, H. G. Selnick, R. E. Zelle, M. P. DeNinno, *J. Am. Chem. Soc.* **1988**, *110*, 4368–4378.

[18] The stereochemistry was controlled by a steric factor rather than an orientation of the neighboring hydroxy group; see ref. [9d].

[19] N. Yamamoto, T. Nishikawa, M. Isobe, *Synlett* **1995**, 505–506.

[20] P. H. Carisen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936–3938.

[21] Determination of the configuration at the C9 position is included in the Supporting Information.

[22] J. Petrov, I. Atanassova, A. Balabanova, N. Mollov, *Izv. Khim.* **1990**, *23*, 53–57.

[23] Detailed analysis of the crude product revealed that one of the products lacked H9, indicating that an oxidation occurred at the C9 position. Kishi et al. reported on the lability of the acetoxy group at the C9 position in their total synthesis of tetrodotoxin. See: a) ref. [9b]; b) H. Tanino, S. Inoue, M. Aratani, Y. Kishi, *Tetrahedron Lett.* **1974**, 335–338.

[24] M. Xie, D. A. Berges, M. J. Robins, *J. Org. Chem.* **1996**, *61*, 5178–5179.

[25] K. Mori, M. Tominaga, T. Takigawa, M. Matsui, *Synthesis* **1973**, 790–791.

[26] Pyridine was indispensable in this addition, while we used DMF in our model studies.[13b]

[27] In this specific case, acetic anhydride was an indispensable solvent. This reaction was much slower or unreproducible when a mixture of acetic anhydride and triethylamine was employed as in our previous (successful) model studies.[13b]

[28] 4-*epi*- and 4,9-Anhydrotetrodotoxins have been found as minor constituents with tetrodotoxins from natural sources.[1, 3a, 3c] For example, 5,6,11-trideoxytetrodotoxin was also isolated with 4-*epi*-trideoxytetrodotoxin in the ratio (ca. 1:1.2).[3a] Compound **22** is the first example of 4,9-anhydrotetrodotoxin among a series of 5-deoxytetrodotoxin analogues.

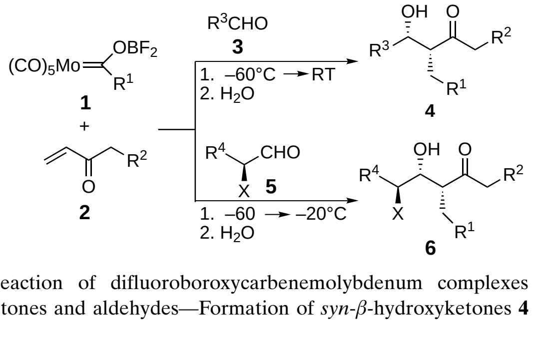
Regio- and Diastereoselective Aldol Products through Three-Component Coupling Reactions of Difluoroboroxy Fischer Carbene Molybdenum Complexes[**]

José Barluenga,[*] Félix Rodríguez,
Francisco J. Fañanás, and Eduardo Rubio

The formation of a large number of carbon–carbon bonds with high efficiency in the minimal number of chemical steps is the requirement of modern synthetic design.[1] In this context, radical and carbanion chemistry has become a valuable tool in organic synthesis. However, both reactive intermediates can be used in a complementary manner and sequential reactions have been devised to prepare complex molecules.[2, 3] On the other hand, despite the importance of Fischer carbene complexes for the development of novel organic transformations[4] there is only a very limited number of examples in which these complexes have been used as precursors of radicals. Thus, tetramethylammonium acyl chromate complexes are adequate precursors for alkyl and acyl radicals, which are formed by oxidation with manganese(III)[5] and copper(II)[6] salts.

In 1997 we reported a simple method for generating acyl radicals from difluoroboroxy Fischer carbene molybdenum complexes in very mild reaction conditions and in the absence of an oxidant.[7] Herein we describe a sequential radical-anionic three-component coupling reaction of difluoroboroxy Fischer carbene molybdenum complexes, vinyl ketones, and aldehydes to give *syn*-β-hydroxyketones diastereoselectively. This process is amenable for synthesizing enantiomerically pure compounds.

The treatment of pentacarbonyl(difluoroboroxycarbene)-molybdenum complexes **1** (formed by reaction of lithium pentacarbonyl acyl molybdate and boron trifluoride diethyl ether complex)[7] with vinyl ketones **2** and aldehydes **3** in diethyl ether at temperatures from -60 to 20 °C led to β-hydroxyketones **4**. According to the NMR studies the *syn* products were formed exclusively (Scheme 1 and Table 1).[3a, 8]



Scheme 1. Reaction of difluoroboroxycarbenemolybdenum complexes with vinyl ketones and aldehydes—Formation of *syn*-β-hydroxyketones **4** or **6**.

---

[*] Prof. Dr. J. Barluenga, Dr. F. Rodríguez,
Dr. F. J. Fañanás, Dr. E. Rubio
Instituto Universitario de Química
Organometálica “Enrique Moles”
Unidad Asociada al CSIC, Universidad de Oviedo
Julian Clavería 8, E-33071-Oviedo (Spain)
Fax: (+349) 8-510-34-50.
E-mail: barluenga@sauron.quimica.uniovi.es

[**] This work was supported by DGICYT (Grant PB97–1271).

Table 1. Synthesis of *syn*-β-hydroxyketones **4** and **6** from carbene complexes **1**, vinyl ketones **2**, and aldehydes **3** and **5**, respectively.

carbene complex	R^1	vinyl ketone	R^2	aldehyde	R^3	R^4	X	Product	Yield [%][a]	*de* [%][b]
1a	c-C_5H_9	**2a**	H	**3a**	Pr	–	–	**4a**	48	–
1a	c-C_5H_9	**2a**	H	**3c**	2-Fu[c]	–	–	**4b**	50	–
1b	*i*Pr	**2a**	H	**3a**	Pr	–	–	**4c**	54	–
1b	*i*Pr	**2a**	H	**3b**	Ph	–	–	**4d**	49	–
1b	*i*Pr	**2a**	H	**3c**	2-Fu	–	–	**4e**	51	–
1b	*i*Pr	**2b**	Bu	**3c**	2-Fu	–	–	**4f**	44	–
1c	Bu	**2a**	H	**3a**	Pr	–	–	**4g**	32[d]	–
1b	*i*Pr	**2a**	H	**5a**	–	Me	OBn	**6a**[e]	43	78
1b	*i*Pr	**2a**	H	**5b**	–	Me	NBn_2	**6b**	42	> 99
1b	*i*Pr	**2b**	Bu	**5b**	–	Me	NBn_2	**6c**	37	> 99
1b	*i*Pr	**2b**	Bu	**5c**	–	Bn	NBn_2	**6d**	36	> 99
1a	c-C_5H_9	**2a**	H	**5c**	–	Bn	NBn_2	**6e**	34	> 99

[a] Based on $[Mo(CO)_6]$. [b] Determined by ^1H NMR spectroscopy of the crude product. [c] 2-Fu = 2-furyl. [d] Nonane-2,5-dione (25 %) was also isolated. [e] Both diastereoisomers have been isolated.

As a consequence of the complete *syn* diastereoselectivity observed for **4** in all the cases examined we carried out a set of experiments using chiral aldehydes **5** to study the diastereofacial selectivity of this process. Thus, the reagents were mixed at – 60 °C, and then the reaction mixture allowed to warm up to – 20 °C, and kept at this temperature for 72 hours (Scheme 1 and Table 1). From this procedure we found diastereoselectivities above 99 % in most cases. A lower selectivity was observed only for **6a**. In this case, the absolute configuration of the new stereogenic centers in the major diastereoisomer of **6a** was determined from the $\Delta\delta$ values ($\delta_{S\text{-MTPA}} - \delta_{R\text{-MTPA}}$) obtained for the MTPA esters **7** (Figure 1).[9] The configurational assignment for compounds **6b** – **e** was made on the basis of the following transformations on **6e**. First, we prepared diol **8** by reduction with lithium aluminium hydride. The relative configuration of C(2)-C(4) was clear from NMR studies on the corresponding acetonide **9** (prepared by treatment of **8** with 2,2-dimethoxypropane and pyridinium-*p*-toluene sulfonate (PPTS) as catalyst). Thus, the high difference in chemical shift between the C(2) methyl groups ($\Delta\delta = 10.4$), the chemical shift of the acetal carbon atom ($\delta = 98.9$), together with the observed NOEs between H(4) and H(6) and the upfield C(2) methyl group correspond to a chair conformation with a 1,3-*syn* disposition of H(4) and H(6) (Figure 1).[10, 11]

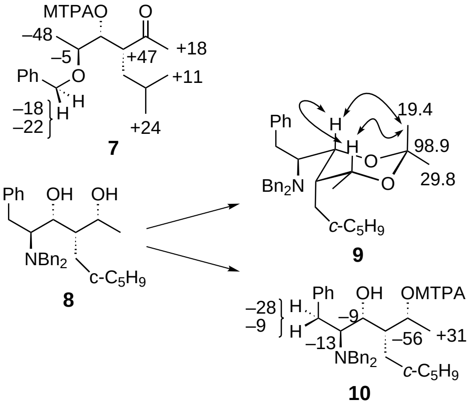
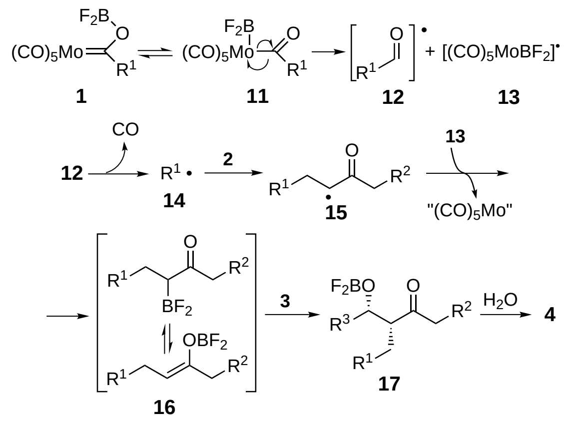


Figure 1. Diagnostic NMR data for **9** and $\Delta\delta$ values ($\delta_S - \delta_R$) for the (S) and (R)-MTPA esters of **7** (at 300 MHz) and **10** (at 400 Mhz). Selected NOEs observed are indicated by arrows. Bn = benzyl; MTPA = α-methoxy-α-(trifluoromethyl)phenylacetic acid.

Finally, the absolute configuration of diol **8** was established as above through the $\Delta\delta$ values of the mono-MTPA esters **10** (Figure 1).[9, 11]

A plausible mechanism that explains the formation of β-hydroxyketones **4** is outlined in Scheme 2. Thus, the equilibrium between the tautomeric species **1** and **11** is shifted towards **11**, presumably as a consequence of a favorable interaction between the boron and the molybdenum atoms,[7, 12] which leads to the acyl radicals **12** and the radical species **13** after the homolytic scission of the carbon – molybdenum bond. These acyl radicals **12** surprisingly undergo decarbonylation[13] to generate the alkyl radicals **14**,[14] which then add to vinyl ketones **2** to generate the radical intermediates **15**. Further electron transfer from **13** to intermediate **15** with loss of the $Mo(CO)_5$ fragment produces boron enolates **16**, which afford the adducts **17** on addition to aldehydes **3**. Finally, hydrolysis of **17** leads to the β-hydroxyketone derivatives **4**. An explanation of the 1,2-*syn* induction in the aldol reaction is possible on the basis of the well known Zimmermann – Traxler chairlike transition state model[15] if the geometry of the formed enolate is assumed to be exclusively *Z*. In our case, the small size of the fluorine atoms would favor the formation of the *Z* isomer.[8b, 16]



Scheme 2. Mechanism proposed for the formation of *syn*-β-hydroxyketones **4** and **6**.

The preference for the Felkin-type products (3,4-*anti*) when chiral aldehydes **5** were used can be accounted for by assuming a nonchelated transition state,[17] as observed in similar reactions.[18] These results reflect a very high degree of substrate control in the aldol addition of achiral boron enolates to chiral aldehydes.[18]

It is worth pointing out that the three-component coupling reaction described here represents an interesting alternative to the aldol reaction where the main problem of the lack of regioselectivity for nearly symmetrical ketones is solved (Figure 2). Further studies on the mechanism and synthetic applications of this novel transformation will be reported in due course.

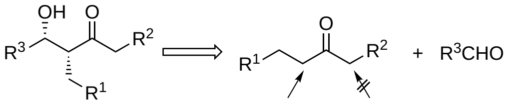


Figure 2. Regio and diastereoselective aldol reaction.

Experimental Section.

Preparation of **4** and **6**: BF$_3$ · OEt$_2$ (0.36 mL, 3 mmol) was slowly added at −60 °C to a solution of **1**, generated by reaction of hexacarbonylmolybdenum (3 mmol) and the corresponding organolithium compound (3 mmol), in diethyl ether (30 mL), and the mixture stirred for 10 min. The vinyl ketone **2** and the aldehyde **3** or **5** were then added dropwise at the same temperature. Stirring was continued while the temperature reached room temperature (compounds **4**) or −20 °C (compounds **6**). The mixture was hydrolyzed with water (30 mL), extracted with diethyl ether (3 × 10 mL), and the organic layer dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the crude product purified by column chromatography (silica gel, hexane/ethyl acetate 40/1). All compounds gave satisfactory analytical data, including elemental analysis, mass and NMR spectra.

Received: May 17, 1999 [Z13425IE]
German version: *Angew. Chem.* **1999**, *111*, 3272–3274

Keywords: carbene complexes · C-C coupling · molybdenum · radical reactions · synthetic methods

---

[1] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) T.-L. Ho, *Tandem Reactions in Organic Synthesis*, Wiley, New York, **1992**; c) L. F. Tietze, *Angew. Chem.* **1993**, *105*, 137; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131; d) N. Hall, *Science* **1994**, *226*, 32.

[2] For some reviews of representative examples of serial processes with different intermediates, see a) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223; b) M. Malacria, *Chem. Rev.* **1996**, *96*, 289; c) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307; d) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339.

[3] For some representative examples, see a) K. Nozaki, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403; b) D. P. Curran, M. J. Totleben, *J. Am. Chem. Soc.* **1992**, *114*, 6050; c) D. P. Curran, T. L. Fevig, C. P. Jasperse, M. J. Totleben, *Synlett.* **1992**, 943; d) B. S. Bronk, S. J. Lippard, R. L. Danheiser, *Organometallics* **1993**, *12*, 3340; e) G. A. Molander, J. A. McKie, *J. Org. Chem.* **1995**, *60*, 872; f) K. Takai, T. Ueda, N. Ikeda, T. Moriwake, *J. Org. Chem.* **1996**, *61*, 7990; g) K. Takai, N. Matsukawa, A. Takahashi, T. Fujii, *Angew. Chem.* **1998**, *110*, 160; *Angew. Chem. Int. Ed.* **1998**, *37*, 152.

[4] a) K. H. Dötz, *Angew. Chem.* **1984**, *96*, 573; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 587; b) K. H. Dötz in *Organometallics in Organic Synthesis: Aspects of a Modern Interdisciplinary Field* (Eds.: H. tom Dieck, A. de Meijere), Springer, Berlin, **1988**; c) W. D. Wulff in *Comprehensive Organic Synthesis*, *Vol. 5* (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, New York, **1991**, p. 1065; d) M. P. Doyle in *Comprehensive Organometallic Chemistry II*, *Vol. 12* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, p. 387; e) W. D. Wulff in *Comprehensive Organometallic Chemistry II*, *Vol. 12* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, p. 469; f) L. S. Hegedus in *Comprehensive Organometallic Chemistry II*, *Vol. 12* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, p. 549.

[5] K. Narasaka, H. Sakurai, *Chem. Lett.* **1993**, 1269.

[6] H. Sakurai, K. Narasaka, *Chem. Lett.* **1994**, 2017.

[7] J. Barluenga, F. Rodríguez, F. J. Fañanás, *Organometallics* **1997**, *16*, 5384.

[8] The relative stereochemistry of **4** was assigned from the reported coupling constant (ca. 6 Hz). See a) C. H. Heathcock, C. T. Buse, N. A. Kleschick, M. C. Pirrung, J. E. Sohn, J. Lampe, *J. Org. Chem.* **1980**, *45*, 1066; b) D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, *103*, 3099.

[9] I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.

[10] S. D. Rychnovsky, B. Rogers, G. Yang, *J. Org. Chem.* **1993**, *58*, 3511.

[11] K. Kouda, T. Ooi, T. Kusumi, *Tetrahedron Lett.* **1999**, *40*, 3005.

[12] J. Barluenga, F. Rodríguez, J. Vadecard, M. Bendix, F. J. Fañanás, F. López-Ortiz, *J. Am. Chem. Soc.* **1996**, *118*, 6090.

[13] I. Ryu, N. Sonoda, *Angew. Chem.* **1996**, *108*, 1140; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1050.

[14] This decarbonylation process is highly dependent on the structure of the radicals formed; thus for primary radicals (R^1 = Bu, carbene **1c** in Table 1) decarbonylation is a slower process and the trapping of **12** with **2** competes with the formation of **14**.

[15] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920.

[16] D. A. Evans, E. Vogel, J. V. Nelson, *J. Am. Chem. Soc.* **1979**, *101*, 6120.

[17] a) M. T. Reetz, *Angew. Chem.* **1984**, *96*, 542; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556; b) M. T. Reetz, *Angew. Chem.* **1991**, *103*, 1559; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531.

[18] a) C. Genari, A. Bernardi, S. Cardani, C. Scolastico, *Tetrahedron* **1984**, *40*, 4059; b) M. T. Reetz, E. Rivadeneira, C. Niemeyer, *Tetrahedron Lett.* **1990**, *31*, 3863; c) C. Genari, D. Moresca, A. Vulpetti, G. Pain, *Tetrahedron Lett.* **1994**, *35*, 4623; d) C. Genari, G. Pain, D. Moresca, *J. Org. Chem.* **1995**, *60*, 6248; e) M. T. Reetz, *Chem. Rev.* **1999**, *99*, 1121.

High-Yielding Enantioselective Synthesis of the Macrolactam Aglycon of Sch 38516 from Two Units of (2*R*)-2-Ethyl-4-penten-1-ol**

Manuel Martín, Gemma Mas, Fèlix Urpí,* and Jaume Vilarrasa*

Dedicated to Professor Elias J. Corey and in memory of Felix Serratosa

The tridecanelactam antifungal agents Sch 38516, Sch 38518, and Sch 39185 isolated by researchers at Schering–Plough[1] from *Actinomadura vulgaris*, shown to be active

---

[*] Prof. F. Urpí, Prof. J. Vilarrasa, M. Martín, G. Mas
Departament de Química Orgànica
Facultat de Química, Av. Diagonal 647
Universitat de Barcelona
E-08028 Barcelona (Spain)
Fax: (+349) 3-339-7878
E-mail: vilarrasa@gsaa1.qo.ub.es

[**] Financial support from the Ministerio de Educación y Ciencia (grants SAF93-0201 and PM95-0061, and doctorate studentship to M.M. from 1994 to 1997) and from the Generalitat de Catalunya (GRQ93-1096 and 1996SGR0102) is acknowledged. Preliminary studies by D. García (1992), with the collaboration of Dr. M. Bartra as supervisor, deserve to be mentioned as well. Thanks are also due to Dr. L. González for obtaining a sample of iodo derivative **9** and to Dr. A. González for the preparation of **11**.