Available online at www.sciencedirect.com
SCIENCE DIRECT
Carbohydrate Research 341 (2006) 1052–1056
Carbohydrate RESEARCH

Note

An efficient synthesis of 2,3-dideoxy-α,β-unsaturated carbohydrate enals by mixed Lewis acid ($HfCl_4$ and ZnI_2) catalyzed hydration of glycals ☆

Mohammad Saquib, Ram Sagar and Arun K. Shaw*

Division of Medicinal and Process Chemistry, Central Drug Research Institute (CDRI), Lucknow 226 001, India

Received 22 December 2005; received in revised form 21 February 2006; accepted 23 February 2006
Available online 29 March 2006

Abstract—A new, efficient method has been developed for converting acyl-, arylalkyl- and alkyl-protected glycals into corresponding 2,3-dideoxy-α,β-unsaturated carbohydrate enals utilizing the in situ generated push–pull effect resulting from the synergistic combination of $HfCl_4$ and ZnI_2 in catalytic amounts. This new procedure eliminates the use of highly toxic Hg^{2+} ions and acidic conditions (0.01–0.02 N H_2SO_4), besides radically shortening the reaction time.

Keywords: α,β-Unsaturated carbohydrate enals; Glycals; Hafnium tetrachloride; Zinc iodide; Push–pull effect

Carbohydrates are ubiquitous and vital biomolecules that can be fashioned into a variety of versatile intermediates used for the synthesis of biodynamic molecules. 2,3-Dideoxy-α,β-unsaturated sugar aldehydes (**2**), commonly known as Perlin aldehydes,[1] constitute an increasingly important class of carbohydrate derivatives that have been used as precursors for the syntheses of many biologically important compounds during the last three decades.[1c,2–4] Until now, Perlin aldehydes have been prepared from the corresponding glycals either by Perlin's method[1a] or its many variants[1b,c] involving Hg^{2+} ion and 0.01N–0.02 N H_2SO_4 to effect the transformation. All these methods thus suffer from the drawback of using the highly toxic Hg^{2+} ion which is not recommended in medicinal chemistry and is also unpopular due to waste-disposal problems. Further, the use of 0.01–0.02 N H_2SO_4 requires the neutralization of the reaction mixture with a base, which in the case of acetyl-protected Perlin aldehydes invariably results in a 1:1 mixture of isomeric products which seriously limits their synthetic utility.[2c,3c,5] In addition (2*E*)-4,6-di-*O*-benzyl-2,3-dideoxy-aldehydo-D-*erythro*-hex-2-enose (**2a**), an important intermediate, could not be synthesized by reported methods in more than 50% yield.[1c] Our research group has been using Perlin aldehydes **2** for preparation of antitubercular compounds.[2e–g] Therefore, it has long been our desire to develop an alternative method for synthesis of Perlin aldehydes **2**. We herein report an efficient and quicker method for the synthesis of Perlin aldehydes from acyl- and alkyl/arylalkyl-protected glycals **1** using benign reagents. Lewis acids are known to efficiently catalyze a number of varied reactions of glycals, including the Ferrier rearrangement.[6] This prompted us to explore Lewis acids as possible catalysts for the hydration of glycals to Perlin aldehydes. Of late $HfCl_4$ has emerged as a versatile Lewis acid.[7] Its high catalytic activity due to larger radii of Hf,[8] low toxicity[9a–c] and relatively greater degree of water tolerance induced us to explore this promising catalyst for our current studies in water and acetonitrile.[10]

The study was initiated by stirring a mixture of 3,4,6-tri-*O*-benzyl-D-glucal (**1a**, 104 mg, 0.25 mmol) and $HfCl_4$ (8 mg, 0.025 mmol) at 110–120 °C in 1:1 CH_3CN–H_2O. The reaction was completed in ~2.5 h

☆ CDRI Communication No. 6855.
* Corresponding author. E-mail: akshaw55@yahoo.com

0008-6215/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2006.02.031

(TLC). The ^{1}H NMR spectrum of the crude product showed that Perlin aldehyde **2a** was formed only in traces. We performed several trial experiments using different quantities of $HfCl_4$ in different proportions of CH_3CN–H_2O mixtures at different temperatures, but better results were not obtained.

At this juncture, we decided to use a combination of two Lewis acids hoping to invoke the push–pull effect[11] for making this transformation more facile. Since glycals are cyclic vinyl ethers having leaving group at C-3 either in the form of an ester or an alkoxy group, we assumed that $HfCl_4$ like $TiCl_4$ would coordinate with the acetoxy or alkoxy group[7a] making it a better leaving group. This process may become more pliant if a group or an atom showing dual character of a good nucleophile and leaving group concurrently adds on to C-1 of the glycal molecule pushing the π bond from C-1–C-2 to C-2–C-3. This would cause elimination of the leaving group at C-3, which itself is being instantaneously substituted by a molecule of water to form the hemiacetal, which then equilibrates with the open-chain α,β-unsaturated (*Z*) aldehyde that ultimately isomerizes to the more stable (*E*) enal.[12] Accordingly for acting at the olefinic bond we decided to use either CdI_2 or ZnI_2 (Zn, Cd and Hg belong to the same group). Both of these showed almost identical results, but our choice fell upon ZnI_2 which is nontoxic[9d] and dissociates in water or polar organic solvents to a greater extent to furnish Zn^{2+} and I^- ions.

Considering all these aspects on carefully optimizing the various parameters one by one, we found that on stirring the substrate **1a** (104 mg, 0.25 mmol) with $HfCl_4$ (18 mg, 0.056 mmol) and ZnI_2 (7 mg, 0.022 mmol) in a 7:3 CH_3CN–H_2O in a temperature range of 135–140 °C (oil bath) for 2.5 h furnished Perlin aldehyde **2a** and some other minor side products, including the 2-deoxy derivative **3a** in approximately 4:1 ratio[†] (Table 1, entry 1). Acetylation of the crude product mixture, followed by column chromatography, gave the acetyl derivative of the Perlin aldehyde **2a** in 72% yield (Scheme 1, Table 1, entry 1).

In the case of benzyl-protected arabinal **1c** and methyl-protected glucal **1d**, the Perlin aldehydes were obtained exclusively by adopting the same methodology as mentioned above for **1a** (Table 1, entries 3 and 4).

Use of the same methodology in case of 3,4,6-tri-*O*-benzyl-D-galactal (**1b**) yielded a 1:2 mixture of Perlin aldehyde **2b** and 2-deoxy pyranose **3b**.[†] After performing several trial experiments on **1b**, the best result obtained was the formation of a 1:1 mixture of Perlin aldehyde **2b** and 2-deoxy sugar derivative **3b**[†] by stirring **1b** (104 mg, 0.25 mmol) with $HfCl_4$ (18 mg, 0.056 mmol) and ZnI_2 (7 mg, 0.022 mmol) in 7:3 CH_3CN–H_2O as solvent in a preheated oil bath at 130–135 °C for 2 h (Table 1, entry 2).

Acetylation of the crude product mixture, followed by column chromatography, gave 43% of the Perlin aldehyde **2b** and 45% of the 2-deoxy product **3b** as their acetyl derivatives. Under identical conditions, 3,4,6-tri-*O*-methyl-D-galactal **1e** furnished **2e** (53%) and **3e** (29%) as their acetyl derivatives. Higher temperature did not lead to any increase in the proportion of Perlin aldehyde; on the contrary, the overall yield was decreased, probably due to degradation of the starting material.

Lowering the oil bath temperature to below 120 °C led to a noticeable decrease in the proportion of Perlin aldehyde **2**. Any further increment of the amount of the reagents in the same ratio had no visible effect on the product formation. It is worth reporting that none of the alkyl/arylalkyl-protected glycals underwent the title reaction to furnish the desired aldehyde, either in the presence of $HfCl_4$ or ZnI_2 alone.

This protocol was also extended to acyl-protected glycals. Since the acyl group is a better leaving group than either the OBn or OMe group, we first wanted to see the effect of $HfCl_4$ alone on the acyl-protected glycals. On stirring a mixture of 3,4,6-tri-*O*-acetyl-D-glucal **1f** (136 mg, 0.5 mmol) and $HfCl_4$ (18 mg, 0.056 mmol) in CH_3CN in a temperature range of 105–110 °C, the reaction was completed (TLC) in 90 min. The ^{1}H NMR spectrum of the worked-up product showed exclusive formation of **2f**. When the same reaction was carried out using 3,4,6-tri-*O*-acetyl-D-glucal **1f** (136 g, 0.5 mmol), $HfCl_4$ (18 mg, 0.056 mmol) and ZnI_2 (7 mg, 0.022 mmol), and the temperature of the oil bath was raised rapidly from room temperature to 110 °C, the reaction was completed in only 6–8 min (TLC). ^{1}H NMR of the worked-up reaction mixture showed exclusive formation of **2f** that could be used as such for further reactions. As the reaction was carried out in very weakly acidic conditions, washing of the reaction mixture with water sufficed eliminating the need for the use of alkali for neutralization of the reaction mixture that solved the problem of acyl group migration. Acetylation of the worked-up product **2f**, followed by column chromatography, furnished its pure triacetate derivative in 74% yield (Table 1, entry 6). The reaction did not proceed with ZnI_2 alone. Similar results were obtained for the other acyl-protected glycals **1g** and **1h** by adopting the same methodology as mentioned above for **1f** (Table 1, entries 7 and 8).

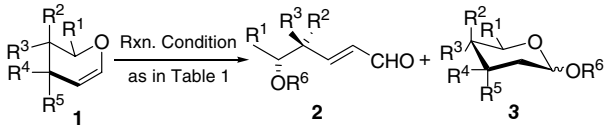
In conclusion, this paper describes a new and efficient method for the preparation of 2,3-dideoxy-α,β-unsaturated sugar aldehydes **2** from their corresponding glycals **1**, eliminating the use of highly toxic Hg^{2+} and acidic conditions by using inexpensive, benign reagents like $HfCl_4$ and ZnI_2 and very mildly acidic conditions. The simpler workup procedure solves the problem of acyl

[†] The ratio was determined from the ^{1}H NMR spectrum of the crude product mixture.

Table 1. Results of Perlin hydrolysis of benzyl/methyl/acyl-protected glycals using $HfCl_4$ (0.056 mmol) and ZnI_2 (0.022 mmol) in a 7:3 CH_3CN–H_2O solvent mixture

Entry	Substrate	Rxn. temp. (°C)	Rxn. time	Product	Product ratio[a] **2**:**3**	Yield (%) **2**	Ref.[b]
1	**1a**	135–140	2.5 h	**2a** and **3a**	4:1	72[c]	1c
2	**1b**	130–135	2.0 h	**2b** and **3b**	1:1	43[c]	1c
3	**1c**	135–140	2.3 h	**2c**	—	85	2c
4	**1d**	135–140	2.5 h	**2d**	—	90	1c
5	**1e**	130–135	2.0 h	**2e** and **3e**	3:2	53[c]	New
6	**1f**	Rt→110	6–8 min	**2f**	—	74[c]	1a
7	**1g**	Rt→110	6–8 min	**2g**	—	73[c]	2j
8	**1h**	Rt→110	6–8 min	**2h**	—	67[c]	2j

[a] The ratios were determined from the ^1H NMR spectra of the crude product mixtures.
[b] References are to known compounds.
[c] Isolated yields after acetylation of the product mixture.



	R^1	R^2	R^3	R^4	R^5	R^6
a	CH_2OBn	H	OBn	OBn	H	H
b	CH_2OBn	OBn	H	OBn	H	H
c	H	H	OBn	H	OBn	H
d	CH_2OCH_3	H	OCH_3	OCH_3	H	H
e	CH_2OCH_3	OCH_3	H	OCH_3	H	H
f	CH_2OAc	H	OAc	OAc	H	H
g	CH_2OAc	OAc	H	OAc	H	H
h	H	H	OAc	H	OAc	H

Scheme 1. Perlin hydrolysis of glycals.

group migration in case of acyl-protected glycals as observed in the Hg^{2+}-catalyzed Perlin hydrolysis.[2c,3c,5] This method thus broadens the synthetic utility of these carbohydrate enals, especially in the field of medicinal chemistry.

1. Experimental

1.1. General methods

All reactions were monitored by thin-layer chromatography (TLC) over silica gel plates. The spots on the TLC plates were visualized by warming the $CeSO_4$ (1% in 2 N H_2SO_4) sprayed plates in an oven at 100 °C. Silica gel (100–200 mesh) was used for column chromatography, and the desired compounds were eluted with an EtOAc–hexane mixture of increasing polarity. IR spectra were recorded on a Perkin–Elmer 881 spectrophotometer, and values are expressed in cm^{-1}. FAB mass spectra (FABMS) were recorded on a JEOL SX 102/DA 6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. HRMS data was recorded on a JEOL MS model JMS-600H mass spectrometer. The calibration was done by using PFK. ^1H NMR and ^{13}C NMR spectra were recorded on an Avance Bruker instrument at 200 MHz for ^1H and 50 MHz for ^{13}C. Chemical shift values are expressed in δ ppm. Optical rotations were determined on Rudolph Autopol III polarimeter using a 1-dm cell at 28 °C; concentrations mentioned are in g/100 mL. Commercial grade CH_3CN containing 0.2% water, purchased from Ranbaxy Fine Chemicals Ltd (India), was used in all experiments.

1.2. Typical procedure for the preparation of 2,3-dideoxy-α,β-unsaturated carbohydrate enals

1.2.1. (2*E*)-4,6-Di-*O*-benzyl-2,3-dideoxy-aldehydo-D-*erythro*-hex-2-enose (2a). To a solution of the benzyl-protected glucal **1a** (104.0 mg, 0.25 mmol) in a mixture of 7:3 CH_3CN–H_2O (10 mL) was added $HfCl_4$ (18.0 mg, 0.056 mmol) and ZnI_2 (7.0 mg, 0.022 mmol). The resulting reaction mixture was heated with stirring in an oil bath at 135–140 °C for 2.5 h. On completion of the reaction, the reaction mixture was quenched with cold water and neutralized with few drops of satd aq $NaHCO_3$. The aqueous layer was extracted with EtOAc (5 × 5 mL). The combined organic layer was dried over Na_2SO_4 and evaporated in vacuo to obtain the crude product mixture **2a** and **3a** in a 4:1 ratio (NMR). This was subjected to acetylation with Ac_2O and pyridine to obtain the chromatographically pure acetyl derivative of **2a** (66.0 mg, 72%).

A similar reaction procedure was adopted for the preparation of compounds **2c** and **2d**.

1.2.2. (2*E*)-4,6-Di-*O*-benzyl-2,3-dideoxy-aldehydo-D-*threo*-hex-2-enose (2b). To a solution of the benzyl-protected galactal **1b** (104.0 mg, 0.25 mmol) in a mixture of 7:3 CH_3CN–H_2O (10 mL) was added $HfCl_4$, (18.0 mg, 0.056 mmol) and ZnI_2 (7.0 mg, 0.022 mmol). The resulting mixture was heated with stirring in a preheated oil bath whose temperature was maintained between 130 and 135 °C for 2 h. On completion of the reaction, the mixture was quenched with cold water and neutralized

with a few drops of satd aq $NaHCO_3$. After separation of the organic layer, the aqueous layer was extracted with EtOAc (5×5 mL). The combined organic layer was dried over Na_2SO_4 and evaporated in vacuo to obtain the crude product mixture **2b** and **3b** in a 1:1 ratio (NMR). This was subjected to acetylation with Ac_2O and pyridine to obtain the chromatographically pure acetyl derivative of **2b** (40.0 mg, 43%).

A similar reaction procedure was adopted for the preparation of compound **2e**.

1.2.3. (2*E*)-4,6-Di-*O*-acetyl-2,3-dideoxy-aldehydo-D-*erythro*-hex-2-enose (2f). To a solution of the acetyl-protected glucal **1f** (136.0 mg, 0.5 mmol) in CH_3CN (7 mL) was added $HfCl_4$ (18.0 mg, 0.056 mmol) and ZnI_2 (7.0 mg, 0.022 mmol). The resulting mixture was heated with stirring in an oil bath whose temperature was raised rapidly from room temperature to 110 °C. On completion of the reaction (6–8 min, TLC control), the reaction was quenched with water. The organic layer was separated, and the aqueous layer was extracted with EtOAc (4×5 mL). The combined organic layer was washed with water 3–4 times, dried over Na_2SO_4 and evaporated in vacuo to obtain the desired aldehyde (90%). This was subjected to acetylation with Ac_2O and pyridine to obtain the chromatographically pure acetyl derivative **2f** (101.0 mg, 74%).

A similar reaction procedure was adopted for the preparation of the compounds **2g** and **2h**.

1.3. Physicochemical and spectral data

1.3.1. (2*E*)-5-*O*-Acetyl-4,6-di-*O*-methyl-2,3-dideoxy-aldehydo-D-*threo*-hex-2-enose (acetyl derivative of 2e). $[\alpha]_D$ +11.5 (*c* 0.130, $CHCl_3$); R_f 0.45 (2:3 EtOAc–hexane); IR (Neat, cm^{-1}): *ν* 2988, 2931 (–C–H str), 2833 (–CHO str), 1744 ($COCH_3$), 1693 (C═O), 1456 (C═C), 1374 (C–H def of $COCH_3$), 1111 (C–O str). ^1H NMR (200 MHz, $CDCl_3$): *δ* 9.55 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1), 6.64 (dd, 1H, $J_{3,2}$ 15.7, $J_{3,4}$ 5.2 Hz, H-3), 6.28 (ddd, 1H, $J_{2,3}$ 15.7, $J_{2,1}$ 7.8, $J_{2,4}$ 1.2 Hz, H-2), 5.09 (m, 1H, H-5), 4.11 (td, 1H, $J_{4,3}$ 5.2, $J_{4,2}$ 1.3 Hz, H-4), 3.64–3.36 (m, 2H, H-6), 3.34 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 2.03 (s, 3H, $COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 193.3 (C-1), 170.7 ($COCH_3$), 152.4 (C-3), 134.0 (C-2), 79.4 (C-4), 72.8 (C-5), 70.6 (C-6), 59.6 and 58.9 ($2 \times OCH_3$), 21.3 ($COCH_3$). FABMS: *m*/*z* 216 $[M]^{+\cdot}$, 202, 180, 154, 136; HRMS: calcd for $C_{10}H_{16}O_5$: *m*/*z* 216.09977; found: *m*/*z* 216.09971.

Acknowledgements

The authors are thankful to Sophisticated Analytical Instrument Facility (SAIF) CDRI Lucknow for providing the spectral data and Mr. Anoop Kishore Pandey, for his technical assistance. M.S. and R.S. are thankful to DOD, New Delhi, for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.02.031.

References

1. (a) Gonzalez, F.; Leasage, S.; Perlin, A. S. *Carbohydr. Res.* **1975**, *42*, 267–274; (b) Mukhopadhyay, A.; Suryawanshi, S. N.; Bhakuni, D. S. *Ind. J. Chem.* **1988**, *27B*, 1009–1011; (c) Sagar, R.; Pathak, R.; Shaw, A. K. *Carbohydr. Res.* **2004**, *339*, 2031–2035, and references cited therein.
2. (a) Tulshian, D. B.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1981**, *103*, 474–475; (b) Rao, A. V. R.; Purandare, A. V.; Reddy, E. R.; Gurjar, M. K. *Synth. Commun.* **1987**, *17*, 1095–1102; (c) Tolstikov, A. G.; Khakhalina, N. V.; Spirikhin, L. V. *Synthesis* **1988**, 221–222; (d) Noshita, T.; Sugiyama, T.; Yamashita, K. *Agric. Biol. Chem.* **1991**, *55*, 1207–1209; (e) Pathak, R.; Shaw, A. K.; Bhaduri, A. P.; Chandrasekhar, K. V. G.; Srivastava, A.; Srivastava, K. K.; Chaturvedi, V.; Srivastava, R.; Srivastava, B. S.; Arora, S.; Sinha, S. *Bioorg. Med. Chem.* **2002**, *10*, 1695–1702; (f) Pathak, R.; Pant, C. S.; Shaw, A. K.; Bhaduri, A. P.; Gaikwad, A. N.; Sinha, S.; Srivastava, A.; Srivastava, K. K.; Chaturvedi, V.; Srivastava, R.; Srivastava, B. S. *Bioorg. Med. Chem.* **2002**, *10*, 3187–3196; (g) Pathak, R.; Shaw, A. K.; Bhaduri, A. P. *Tetrahedron* **2002**, *58*, 3535–3541; (h) Yadav, J. S.; Reddy, B. V. S.; Padmavani, B. *Synthesis* **2004**, 405–408; (i) Yadav, J. S.; Reddy, B. V. S.; Parimala, G.; Raju, A. K. *Tetrahedron Lett.* **2004**, *45*, 1543–1546; (j) Sagar, R.; Singh, P.; Kumar, R.; Maulik, P. R.; Shaw, A. K. *Carbohydr. Res.* **2005**, *340*, 1287–1300.
3. (a) Kaluza, Z.; Chmielewski, M.; Pedersen, E. B. *Heterocycles* **1988**, *27*, 1313–1316; (b) Wengel, J.; Lau, J.; Pedersen, E. B. *Synthesis* **1989**, 829–832; (c) Lau, J.; Wengel, J.; Pedersen, E. B.; Vestergaard, B. F. *Synthesis* **1991**, 1183–1190; (d) Wengel, J.; Pedersen, E. B.; Vestergaard, B. F. *Synthesis* **1992**, 319–322; (e) Singh, S. K.; Parmar, V. S.; Wengel, J. *Tetrahedron Lett.* **1996**, *37*, 7619–7622.
4. Turner, C. I.; Williamson, R. M.; Turner, P.; Sherburn, M. S. *Chem. Commun. (Cambridge)* **2003**, 1610–1611, and references cited therein.
5. Pathak, R. Ph.D Thesis, Dr. B. R. Ambedkar University Agra, India, 2001; p 98.
6. (a) Ferrier, R. J. *Top. Curr. Chem.* **2001**, *215*, 153–175; (b) Ferrier, R. J.; Zubkov, O. A. *Org. React.* **2003**, *62*, 569–736.
7. (a) Dunn, P. J.; Graham, A. B.; Grigg, R.; Higginson, P. *Chem. Commun.* **2000**, 2035–2036; (b) Saito, S.; Nagahara, T.; Yamamoto, H. *Synlett* **2001**, 1690–1692; (c) Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4079–4082; (d) Shiina, I.; Suzuki, M.; Yokoyama, K. *Tetrahedron Lett.* **2002**, *43*, 6395–6398; (e) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8179–8188.

8. Kobayashi, S.; Morikawi, M.; Hachiya, I. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 267–273.
9. (a) Emsley, J. *The Elements*, 3rd ed.; Claredon: Oxford, 1988; (b) Sax, N. I.; Lewis, R. J., Sr. In *Dangerous Properties of Industrial Materials*, 7th ed.; Van Nostrand Reinhold: New York, 1989; Vol. 3, pp 1833–1834; (c) US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. *Registry of Toxic Effects of Chemical Substances (RTECS)*; 2002; (d) Bailar, J. C.; Emeleus, H. J.; Nyholm, R. Sir; Trotman-Dickenson, A. F. In *Comprehensive Inorganic Chemistry*; Pergamon Press: Oxford, 1973; Vol. 3, p 201 and references cited therein.
10. (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023–2035; (b) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741–760.
11. (a) Kocovsky, P. *J. Org. Chem.* **1988**, *53*, 5816–5819; (b) Landini, D.; Maia, A.; Pinna, C. *ARKIVOC* **2004**, 202–212.
12. Madaj, J.; Rak, J.; Sokolowski, J.; Wisniewski, A. *J. Org. Chem.* **1996**, *61*, 2988–2994.