Total Asymmetric Synthesis of Monosaccharides and Analogues

Inmaculada Robina*, Ana T. Carmona, Antonio J. Moreno-Vargas, and Elena Moreno-Clavijo

Abstract: Since the discovery of the ‘formose reaction’ by Butlerow,[1] total synthesis of carbohydrates has undergone rapid development. The most important methods for the asymmetric synthesis of monosaccharides and analogues of biological importance are presented. Nowadays any natural and non-natural monosaccharide can be prepared pure in both enantiomeric forms starting from inexpensive starting materials. Metal-based asymmetric catalysis and organocatalysis have been successfully applied, alone or in combination with chemoenzymatic methods. Alternative methods rely upon substrate- or reagent-controlled diastereo- and enantioselective reactions. Suiably protected carbohydrates have been prepared by total synthesis, thus allowing their direct use in the preparation of oligosaccharides and analogues.[2]

Keywords: Aldolase · Allylation · Asymmetric aldol · Chain elongation · Dihydroxylation · Epoxidation · Hetero-Diels-Alder · Organocatalysis

1. Applications of Chemoenzymatic Methods and Organocatalysis

1.1 Aldolase-catalyzed Asymmetric Aldol Condensations

The enzymatic aldol addition in the presence of type I and II aldolases[3] represents a useful method for the synthesis of various sugars and sugar-like structures.[4] Thus, d- and l-fructose are prepared from dihydroxyacetone monophosphate (DHAP) and d- and l-glyceraldehyde (Scheme 1), in the presence of rabbit muscle aldolase (RAMA) or l-rhamnulose 1-phosphate (Rha) aldolase.[5]

The method also works to generate (–)-1-deoxymannonojirimycin (1) and (+)-1-deoxyribose-5-phosphate aldolase (DERA) condensation between acetaldehyde and racemic 3-thio-glyceraldehyde.[8]

Similarly, pyrrolidines are obtained from 2-azidoaldehydes as substrates in the RAMA-catalyzed aldol reaction with DHAP followed by reduction.[3,7] 2-Deoxy-5-thio-d-erythro-pentose was obtained by catalyzed 2-deoxyribose-5 phosphate aldolase (DERA) condensation between acetaldehyde and racemic 3-thio-glyceraldehyde.[8]

1.2 Asymmetric Synthesis of Carbohydrates Applying Organocatalysis

The List[9] proline-catalyzed intermolecular aldol reaction based on the intramolecular Hajas-Parrish-Eder-Sauer-Wiechert reaction[10] has been widely used in de novo synthesis of carbohydrates. In this reaction, enolizable achiral aldehydes and ketones are transformed into the corresponding enamines, which react with...
less enolizable carbonyl compounds, even in one-pot protocols. A metal-free partial Zimmerman-Traxler-type transition state has been postulated (Fig. 1).[11]

![Fig. 1. Postulated transition state model.](image)

Proline and derivatives,[12] simple amino acids and peptides,[13] and cyclic compounds[14] are effective asymmetric catalysts. Solid-supported proline-terminated peptides have also been used as heterogeneous catalysts for the asymmetric aldol reaction.[15] An improvement of the stereochemical outcome of the reaction by using protected dihydroxyacetone variants such as 1,3-dioxan-5-one and 2,2-dimethyl-1,3-dioxan-5-one with aldehydes in the presence of (S)-proline ((S)-Pro) and (S)-2-pyrrolidin-1-1-tetrazole was reported by Barbas III and co-workers. Reaction of 2,2-dimethyl-1,3-dioxan-5-one (5) with appropriate aldehydes provided access to l-ribulose and d-tagatose (Scheme 3).[16]

Enders and co-workers[17] reported the synthesis of various protected carbohydrates and aminosugars through highly diastereo- and enantioselective direct organocatalytic aldol reactions of 5 with appropriate aldehydes in the presence of (S)-proline. There is a matching correspondence between α-branched (S) or (R)-configured aldehydes and (S) or (R)-proline, respectively. A similar route was reported by Córdova and co-workers,[18] McMillan and co-workers[19] reported the first example of direct enantioselective aldehyde–aldehyde cross-aldol reaction using small molecules as catalysts, e.g. the l-proline-catalyzed aldol reaction generates hexoses.[20] By combining l-erythrose derivative 6 obtained by l-proline-catalyzed dimerization of (t-Bu)PhSiOCH2CHO, with enoxysilane 7 in Mukaiyama aldol reactions catalyzed by various Lewis acids, McMillan and co-workers have realized efficient, two-step synthesis of semi-protected l-glucose (8) and l-mannose (9) (Scheme 4). The method was also applied to l-allose derivatives.[21]

Highly enantioselective double aldol reaction of benzoxycetalddehyde using various α-amino acids as organocatalysts in water was reported by Córdova and co-workers.[22] They also reported tandem two-step iterative aldol reaction with aldehydes for the synthesis of natural/unnatural hexoses (Scheme 5).[23]

Barbas and co-workers reported the preparation of α-aminosugars and derivatives by direct organocatalytic asymmetric aldol reaction of α-aminoaldehydes. For instance, the reaction of 5 with phthalimido aldehyde 10 followed by stereoselective reduction of the carbonyl moiety afforded protected aminoolditol 11 (Scheme 6).[16]

In a similar way, Enders and co-workers have prepared d-erythrod-4-ulos, 5-amino-5-deoxy-l-psicose and 5-amino-5-deoxy-l-tagatose derivatives.[17] The proline-catalyzed Mannich reaction was applied by Barbas and co-workers as depicted in Scheme 7.[24]

A similar reaction was applied by List and co-workers for the synthesis of β-aminocarbonyl compounds.[25]

These reactions exhibit opposite enantiofacial selectivity to the proline-catalyzed aldol reaction. The attack to the si-face is preferred (Scheme 8).

A three-component Mannich reaction with several aldehydes and p-anisidine with l-proline as organocatalyst was used by Enders for the synthesis of aminopenitoses and aminohexoses.[26] This reaction
Dondoni and co-workers have developed highly anti-selective homologation of \( \alpha \)-hydroxycarbaldehydes and \( \alpha \)-hydroxylactones by addition of 2-(trimethylsilyl)lithiazole (16) to chiral aldehydes. From \( \text{D-} \) and \( \text{L-} \)-glyceraldehydes, \( \text{D-} \) and \( \text{L-} \)-erythro configured derivatives are obtained.[34] Chain elongation to the corresponding all-anti configurated monose 17 derivative was performed by iterative additions and unmasking protocols (Scheme 11). Dondoni’s methodology was applied to the preparation of other aldose configurations[35] and all kinds of aminosugars.[36]

Other alternative one-carbon chain elongation of aldoses are the nitroaldol condensation[37] and the methodologies reported by Kusunabe and Sato,[38] and Chikashita and co-workers.[39]

The addition of (+)-(R)-methyl p-tolylsulfoxide to \( \alpha \beta \)-unsaturated esters in the presence of LDA gave the corresponding ketosulfoxides which were reduced into \( \beta \)-hydroxy sulfoxides that were converted into \( \text{L-} \)-arabinitol derivatives. Thus, starting from 19, allylic alcohol 20 was obtained which after dihydroxylation, Pummerer rearrangement and subsequent reduction and acetylation gave thioarabinitol 22 (Scheme 12).[40]

### 2.2 Asymmetric Aldol Reactions

Cross-aldolization of crotonaldehydes (23) and enoxysilane 24 under Mukaiyama conditions gave the corresponding anti-aldols that were further transformed into several sugars as indicated in Scheme 13.[28,41]

Kobayashi and Kawasaki[28b] prepared \( \text{L-} \)-fucose from (E)-crotonaldehyde applying an analogous method.

Conversion of \((\text{R}-\text{HYTRA})^+\)[42] into its lithium enolate and subsequent addition to acrolein gave \((1'R,3R)-\text{26}\) (diastereoselectivity: 92:8) which was transformed into a iodolactone precursor of several 2-deoxyfuranosides 27a–c (Scheme 14).[43]

Diastereoselective aldol reaction of an Evans’ homochiral enolate with crotonaldehyde gave the syn aldol that was transformed into the Weinreb amide, a potential precursor of all kinds of monosaccharides and analogues, including 1-deoxyxojirimycin.[44] Enders and Jegelka prepared enantiomerically pure \( \text{C}_{\text{P}} \) to \( \text{C}_{\text{S}} \)-deoxyxylohydrates using RAMP/SAMP derivatives and 5.[45]

### 2.3 Aldehyde Olefination and Asymmetric Epoxidation

Wittig olefination of \( \text{D-} \)-glyceraldehyde acetone with \( \text{Ph}_{3}\text{P}+\text{CHCHO} \) and reduction of the enal gave the corresponding (E)-allylic alcohol, which upon Katsuki-Sharpless enantioselective epoxidation[46] furnished \( \text{D-} \)-arabinol (= \( \text{D-} \)-lyxitol) and ribitol. Similarly, olefination with \( \text{Ph}_{3}\text{P}+\text{CHCH(OEt)}_2 \), acidic hydrolysis of
the diethyl acetal and subsequent reduction of the enal provided the (Z)-allylic alcohol. Subsequent diastereoselective epoxidation and hydrolysis lead to α-arabinitol or xyitol.[47] The synthesis of all tetrooses and hexoses developed by Sharpless and Masmume uses also the Katsuki-Sharpless asymmetric epoxidation of (E)-allylic alcohols as key-step. The epoxides obtained by oxidation of (E)-4-(O-protected)but-2-en-1-ol underwent a Payne rearrangement in the presence of NaOH, giving terminal epoxides that were opened regioselectively by PhSNa to give phenylsulfides. Protection of the diols as acetonides, oxidation into sulfoxides and Pummerer rearrangement on treatment with Ac₂O and AcONa furnished L- or D-(R,S)-1-O-acetyl-2,3-di-O-isopropylidene-1-phenylthio-4-(O-protected)-erythrose. Subsequent hydrolysis gave the corresponding erythro derivatives. Base-catalyzed isomerization of cis-disubstituted dioxolanes into the more stable trans isomers allows the conversion of (Z)-but-2-ene-1,4-diol into eight tetrooses. By applying an iterative similar route, 16 hexoses were obtained.[48]

2.4 Aldehyde Olefination and Dihydroxylation

Convenient olefination of d-glycer-aldehyde to (E)-3-(2,2-dimethyl-1,3-di-oxolan-4-yl)prop-2-enediol followed by protection as silyl ether and subsequent Sharpless asymmetric dihydroxylation gave other alditol stereomers that can be converted into all kinds of C₅-monoosaccharide derivatives.[49]

2.5 Allylation and Subsequent Ozonolysis

2-Deoxypentoses can be prepared by two-carbon chain elongation of 2,3-O-isopropylidene-d-glyceraldehyde following Roush’s allylation method based on the highly diastereoselective additions of homochiral allylboronates derived from (R,R)- and (S,S)-tartaric acid.[50] For instance, the synthesis of 2-deoxy-d-ribose and 2-deoxy derivative 32 outlined in Scheme 15. Similarly, Roush and Straub[51] obtained 2,6-dideoxyhexose derivatives.

2.6 Hetero-Diels-Alder Additions

The first total synthesis of (+)-KDO is based on the hetero-Diels-Alder addition of α-selenoaldehyde 33 to the α-furyl-substituted diene 34.[52] The reaction gives an adduct mixture which on treatment with CF₃COOH delivers a 5:1 mixture of cis/trans dihydropyrones 35 and 36. Pure 35 was further transformed into (+)-KDO through addition of methanol, benzoylation, oxidative elimination of the phenylseleno group and dihydroxylation followed by benzoylation of the corresponding diol. Final oxidation with RuO₄ followed by esterification with diazomethane and deprotection gave the target KDO (Scheme 16).

Independently, Evans[53] and Jørgensen[54] have shown that β,γ-unsaturated α-keto ester 37 reacts with ethyl vinyl ether 38 in the presence of enantioselectively pure bisoxazoline copper(tl) complex 39 as catalyst. Enantioselectively enriched dihydropyran 40 was thus obtained which was further converted into 2,4-dideoxy-β-D-manno-pyranoside tetraacetate 41 (Scheme 17).[55]

3. Conclusion

Biocatalysis and organocatalysis are opening a large number of possibilities to the total asymmetric synthesis of carbohydrates and analogues. Because of the ease of application and the limited number of synthetic steps required to construct monosaccharides that are dressed up with adequate semi-protection, one can foresee that these catalytic procedures might surpass soon more traditional methodologies based on the delicate chemical derivation of natural carbohydrates. Additionally, an
arsenal of methods is now available for the stereoselective chain elongation of aldehydes and ketones based on substrate or/and reagent control, or on asymmetric aldol reaction enantio-controlled by the chemical catalyst. Alternatively, olefination of aldehydes and subsequent Katsuki-Sharpless asymmetric epoxidation or Sharpless asymmetric dihydroxylation can be used (asymmetry controlled by the catalyst). The procedures can be applied to the construction of complicated monosaccharides and analogues of biological interest. These chemical methods are very well suited to generate long-chain carbohydrates, deoxyaldoses and alditols, aminodeoxy and amidoaldose derivatives.

Acknowledgements

I thank the Ministerio de Ciencia e Innovación of Spain (CTQ2008-01565/BQU) and the Junta de Andalucía (FQM 345) for financial support.

Received: September 9, 2010

[1] a) M. A. Butlerow, CR Séances Acad. Sci. 1861, 53, 145; b) M. A. Butlerow, Ann. Chem. 1861, 30, 295.
[2] For related references see: a) P. Vogel, in ‘Encyclopedia of Glycochemistry’, Eds. B. Fraser-Reid, K. Tatsuta, J. Thiem, Springer, Berlin, 2001, Vol. 2, Chapter 4, pp 1023; b) P. Vogel, in ‘The Organic Chemistry of Sugars’, Eds. D. E. Levy, P. Fugedi, CRC Taylor & Francis Group, Boca Raton, FL, 2006, Chapter 13, pp 629; c) I. Robina, P. Vogel, in ‘Comprehensive Glycochemistry’, Ed. J. Kamerling, Elsevier, Amsterdam, 2006, Vol. 1, pp 489; d) I. Robina, P. Vogel, in ‘Glycochemistry, Chemistry and Chemical Biology’, 2nd ed., Ed. B. Fraser-Reid, K. Tatsuta, J. Thiem, Springer Verlag 2008, 857; e) I. Robina, P. Vogel, Chim. Oggi-Chem. Today 2007, 25, 65; f) I. Robina, P. Vogel, Chim. Oggi-Chem. Today 2007, 25, 100; g) I. Robina, P. Vogel, Chim. Oggi-Chem. Today 2007, 25, 104.
[3] See e.g. C.-C. Hsu, Z. Hong, M. Wada, D. Franke, C.-H. Wong, PNAS 2005, 102, 9122.
[4] a) C. H. Wong, R. L. Halcombe, Y. Ichikawa, T. Kajimoto, Angew. Chem. Int. Ed. 1995, 34, 512; b) H. M. J. Gislen, L. Qiao, W. Fritz, C.-H. Wong, Chem. Rev. 1996, 96, 443; c) S. Takayama, G. J. McGarvey, C.-H. Wong, Chem. Soc. Rev. 1997, 26, 407; d) T. D. Machajewski, C.-H. Wong, Angew. Chem. Int. Ed. 2000, 39, 1352; e) M. G. Silvestri, G. Desamito, M. Mitchell, C.-H. Wong, Topics in Stereochemistry 2003, 23, 267.
[5] D. Franke, T. Machajewski, C.-C. Hsu, C.-H. Wong, J. Org. Chem. 2003, 68, 6828.

Scheme 17. Jørgensen’s asymmetric synthesis of an ethyl β-D-mannopyranoside derivative.
Glycochemistry today

a) A. Dondoni, G. Fantin, M. Fogagnolo, P. Pedrini, J. Org. Chem. 1990, 55, 1439; b) A. Dondoni, D. Perrone, P. Merino, J. Org. Chem. 1995, 60, 8074.

a) A. Dondoni, S. Franco, F. Junquera, F. L. Merchán, P. Merino, T. Tejero, V. Bertolasi, Chem. Eur. J. 1995, 1, 505; b) A. Dondoni, S. Franco, P. L. Merchán, P. Merino, T. Tejero, Tetrahedron Lett. 1993, 34, 5479; c) P. Merino, S. Franco, P. Merchán, T. Tejero, Tetrahedron Lett. 2002, 43, 459; d) A. Dondoni, P. P. Giovannini, D. Perrone, Org. Chem. 2002, 67, 7203.

L. Benzing-Nguyen, M. B. Perry, J. Org. Chem. 1978, 43, 551.

M. Kusakabe, F. Sato, Chem. Lett. 1986, 1473.

H. Chikashita, T. Nikaya, K. Itoh, Nat. Prod. Lett. 1993, 2, 183.

a) G. Solladié, C. Frechou, J. Hutt, G. Demailly, Bull. Soc. Chim. Fr. 1987, 827. b) G. Solladié, G. Demailly, C. Greck, J. Org. Chem. 1985, 50, 1552.

T. Mukaiyama, in ‘Trends in Synthetic Carbohydrate Chemistry, ACS Symposium Series 386’, Eds. D. Horton, L. D. Hawkins, G. D. McGarvey, American Chemical Society, Washington, 1989, Chapter 15, pp 278.

R. Devant, U. Mahler, H. Braun, Chem. Ber. 1988, 121, 397.

S. Gräf, M. Braun, Liebigs Ann. Chem. 1993, 1091.

A. J. Rudge, I. Collina, A. B. Holmes, R. Baker, Angew. Chem. Int. Ed. Engl. 1994, 33, 2320.

a) D. Enders, U. Jegelka, Tetrahedron Lett. 1993, 34, 2453; b) A. Job, C. F. Janeck, W. Beltray, R. Peters, D. Enders, Tetrahedron 2002, 58, 2253.

a) T. Katsoyiannis, K. B. Sharpless, J. Am. Chem. Soc. 1980, 102, 5974; b) A. Pfenninger, Synthesis 1986, 89; c) K. A. Jørgensen, Chem. Rev. 1989, 89, 431.

T. Katsoyiannis, K. B. Sharpless, D. Tuddenham, J. H. Walker, J. Org. Chem. 1982, 47, 1373; b) P. Ma, Y. S. Martin, S. Masamune, K. B. Sharpless, S. M. Viti, J. Org. Chem. 1982, 47, 1378.

S. Y. Ko, A. W. M. Lee, S. Masamune, L. A. Reed III; K. B. Sharpless, F. J. Walker, Tetrahedron 1990, 46, 245.

K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartiung, K.-S. Jung, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, X.-L. Zhang, J. Org. Chem. 1992, 57, 2768; b) H. Becker, K. B. Sharpless, Angew. Chem. Int. Ed. Engl. 1996, 35, 448; c) G. Li, H.-T. Chang, K. B. Sharpless, Angew. Chem. Int. Ed. Engl. 1996, 451; d) M. Jørgensen, E. H. Iversen, R. Madsen, J. Org. Chem. 2001, 66, 4625.

a) W. R. Roush, A. E. Walts, L. K. Hoong, J. Am. Chem. Soc. 1985, 107, 8186; b) W. R. Roush, R. L. Halterman, J. Am. Chem. Soc. 1986, 108, 294.

a) W. R. Roush, J. A. Straub, Tetrahedron Lett. 1986, 27, 3349; b) W. R. Roush, J. A. Hunt, J. Org. Chem. 1995, 60, 798.

S. I. Danishefsky, M. P. DeNinno, S.-H. Chen, J. Am. Chem. Soc. 1988, 110, 3929.

J. Thorhauge, M. Johannsen, K. A. Jørgensen, Angew. Chem. Int. Ed. 1998, 37, 2404.

H. Audrain, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, J. Org. Chem. 2000, 65, 4487.