

HETEROCYCLES, Vol. 65, No. 6, 2005, pp. 1289 - 1294

Received, 2nd March, 2005, Accepted, 14th April, 2005, Published online, 15th April, 2005

DOUBLE DIASTEREOSELECTIVE SYNTHESIS OF *SYN,SYN*-BIS(1,2-ISOXAZOLIN-5-YL)METHANOL AND *SYN,SYN,SYN*-1,2-BIS(1,2-ISOXAZOL-5-YL)ETHANE-1,2-DIOLS: FACILE ROUTE FOR THE SYNTHESIS OF POLYOLS

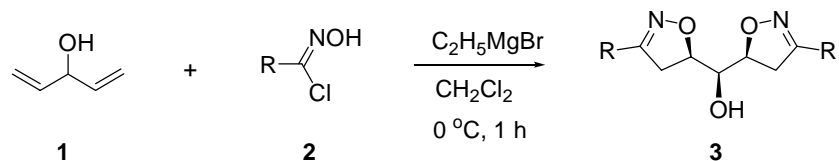
Bum Suk Son, Bo Gan Song, Jung Ki Kim, Min Jung Seo, Zaesung No, and Hyoung Rae Kim*

Medicinal Science Division, Korea Research Institute of Chemical Technology, P. O. Box 107, Yusong, Taejeon 305-600, Korea; E-mail: hyungrk@kriect.re.kr

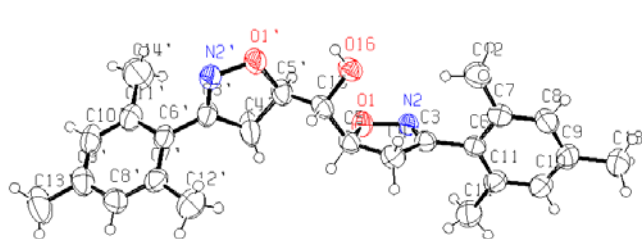
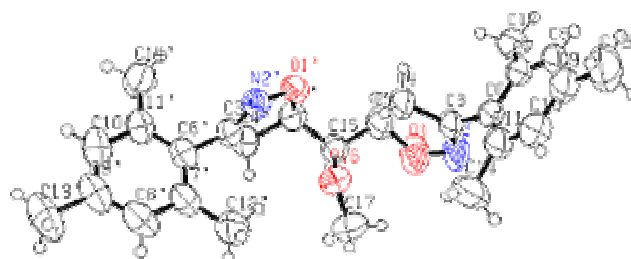
Abstract – *syn, syn*-Bis(1,2-isoxazolin-5-yl)methanols and *syn, syn, syn*-1,2-bis(1,2-isoxazol-5-yl)ethane-1,2-diols were synthesized from various nitrile oxides with 1,4-pentadien-3-ol and 1,5-hexadiene-3,4-diol respectively in the presence of ethylmagnesium bromide by double diastereoselective 1,3-dipolar cycloaddition reaction. The resulting isoxazolines were converted to the corresponding new polyols by hydrogenolysis with Raney Ni.

Many natural products¹ including macrolides showing antibiotic activity contain polyol structures, which have been stimulating the development of efficient chemical methods for their construction.²

Kanemasa *et al.*³ reported 1,3-dipolar cycloaddition reactions of nitrile oxides with allyl alcohols afford exclusively *syn*-adducts by the aid of magnesium chelation effect. We applied this magnesium chelation effect to prepare polyols by the reaction of nitrile oxides with 1,4-pentadien-3-ol and 1,5-hexadiene-3,4-diol followed by the hydrogenation with Raney Ni. When magnesium alkoxides of 1,4-pentadien-3-ol prepared *in situ* by 1.5 equiv. of ethylmagnesium bromide was reacted with various nitrile oxides, *syn, syn*-bis(1,2-isoxazolin-5-yl)methanols were formed as a major products in moderate yields as shown in Scheme 1. Hydroximoyl chlorides were used as precursors of nitrile oxides in the cases of Entries 1, 2, and 5, and in these cases 1.2 equiv. of ethylmagnesium bromide was additionally needed. When diphenylacetone nitrile oxide (Entry 1) and mesitronitrile oxide (Entry 3) were reacted, the *syn, anti*-isomers were isolated as minor product (*syn, syn*/*syn, anti* = 8/2, 9/1 respectively), but in other cases isomers could not be found. The formation of *syn, anti*-isomer seemed to be affected by the of the substituents.



Entry	R	Yield (%)
1		45
2		66
3		63
4		67
5		54

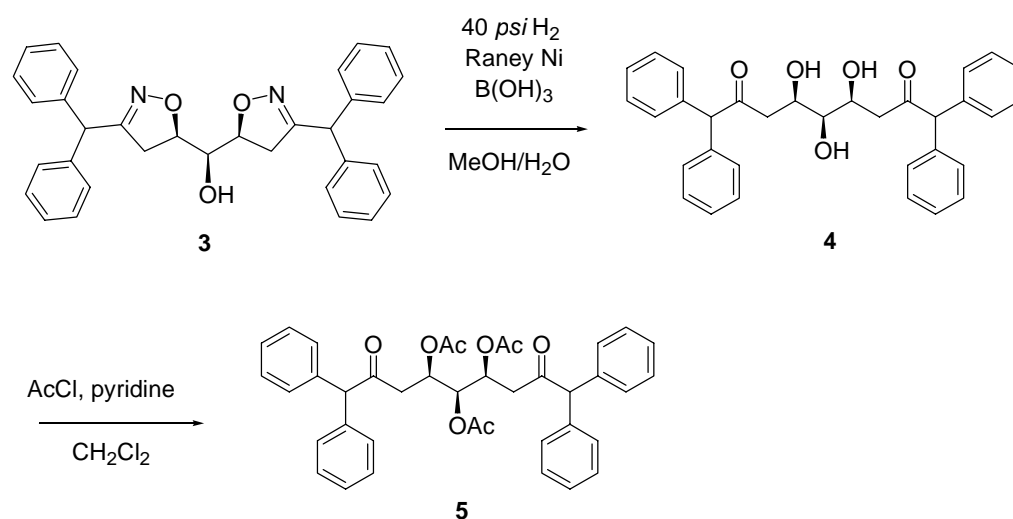
*syn,syn-3**syn,anti-3 (O-methyl)*

Scheme 1

The bulkier the substituent is, the less the stereoselectivity is. We examined the reaction of mesitronitrile oxide without ethylmagnesium bromide, the ratio of *syn,syn* and *syn,anti*-isomer was reversed to be 3 : 7. The resonances of **3** in ^1H NMR spectrum exhibited the existence of symmetric plane but they are not sharp. When we added small amount of D_2O to the NMR tube, the peaks were sharpened. The same phenomenon was observed by *O*-acetylation of **3** (Entry 3), and we concluded the phenomena seemed to come from the deletion of asymmetric hydrogen bonding by *O*-acetylation. The structures of *syn,syn*

and *syn,anti*-isomers were illustrated by the X-Ray crystallography of *syn,syn*-**3** and *O*-methyl-*syn,anti*-**3** (Entry 3) as shown in Scheme 1. The spectral data of **3** were listed in the references.⁴

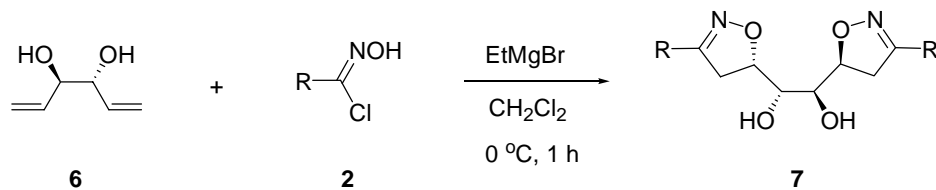
Isoxazoline ring of *syn,syn*-bis(1,2-isoxazolin-5-yl)methanols (**3**, Entry 1) was cleaved by hydrogenation on Raney Ni and the triol (**4**) was formed as shown in Scheme 2. For **4** was easily dehydrated during the purification by silica gel chromatography, we isolated **5** in 65% after acetylation of **4**. ¹H NMR spectra⁵ of **5** also exhibited the existence of symmetric plane. We examined the same reaction with *l*-1,5-hexadiene-3,4-diol (**6**) instead of 1,4-pentadien-3-ol (**1**) and we obtained *syn,syn,syn*-1,2-bis(1,2-isoxazol-5-yl)ethane-1,2-diols (**7**) by clearer reactions in better yields. The diastereomeric isomers could not be observed in these reactions. ¹H NMR spectra⁶ of **7** showed the existence of mirror plane, and the peaks in both sides were overlapped.



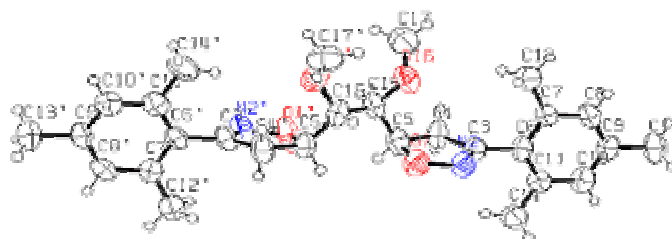
Scheme 2

The 3-D structure of **7** (Entry 3) was confirmed by X-Ray crystallography of *O*-methylated **7** as shown in Scheme 3. In this case, 1.9 equiv. of ethylmagnesium bromide were used for the reaction of nitrile oxides with diol (**6**). When more than 2.0 equiv. of ethylmagnesium bromide were used, the yields were decreased by the formation of unknown impurities.

In conclusion, *syn,syn*-bis(1,2-isoxazolin-5-yl)methanols and *syn,syn,syn*-1,2-bis(1,2-isoxazol-5-yl)-ethane-1,2-diols were synthesized from various nitrile oxides with 1,4-pentadien-3-ol and 1,5-hexadiene-3,4-diol respectively in the presence of ethylmagnesium bromide by double diastereoselective 1,3-dipolar cycloaddition reaction. The resulting isoxazolines seem to be useful for the synthesis of new chiral polyols by the reductive cleavage of isoxazoline rings.



Entry	R	Yield (%)
1		63
2		68
3		76



syn,syn-7(dimethoxy)

Scheme 3

ACKNOWLEDGEMENTS

This research was supported financially by a grant (CBM2-A500-001-2-1-0) from the Center for Biological Modulators of the 21th Centry Frontier R&D Program.

REFERENCES AND NOTES

1. I. Kimura, Y. Ota, R. Kimura, T. Ito, Y. Yamada, Y. Kimura, Y. Sato, H. Watanabe, Y. Mori, K. Harada, and M. Suzuki, *Tetrahedron Lett.*, 1987, **28**, 1921; H. Nakamura, T. Asari, and A. Murai, *J. Am. Chem. Soc.*, 1995, **117**, 550; H. Murata, I. Ohama, K. Harada, M. Suzuki, T. Ikemoto, T. Shibuya, T. Haneishi, A. Torikata, Y. Ikezono, and N. Nakayama, *J. Antibiotics*, 1995, **48**, 850; H.

- Murata, K. Suzuki, T. Tabayashi, C. Hattori, Y. Takada, K. Harada, M. Suzuki, T. Ikemoto, T. Shibuya, T. Haneishi, A. Torikata, Y. Ikezono, and N. Nakayama, *J. Antibiotics*, 1995, **48**, 838; H. Nakamura, M. Takahashi, and A. Murai, *Tetrahedron: Asymmetry*, 1998, **9**, 2571; J. Krueger and E. M. Carreira, *Tetrahedron Lett.*, 1998, **39**, 7013; R. K. Boeckman Jr., T. J. Clark, and B. C. Shook, *Helv. Chim. Acta*, 2002, **85**, 4532.
2. T. Nakata, T. Suenaga, and T. Oishi, *Tetrahedron Lett.*, 1989, **30**, 6525; S. D. Rychnovsky, *J. Org. Chem.*, 1989, **54**, 4982; A. Dondoni and P. Merino, *Synthesis*, **1993**, 903; K. Tanino, N. Yoshitani, F. Moriyama, and I. Kuwajima, *J. Org. Chem.*, 1997, **62**, 4206; D. Enders and T. Hundertmark, *Tetrahedron Lett.*, 1999, **40**, 4169; S. A. Burova and F. E. McDonald, *J. Am. Chem. Soc.*, 2002, **124**, 8188; D. Liu and S. A. Kozmin, *Org. Lett.*, 2002, **4**, 3005.
3. S. Kanemasa, M. Nishiuchi, A. Kamimura, and K. Hori, *J. Am. Chem. Soc.*, 1994, **116**, 2324; S. Kanemasa, S. Kobayashi, M. Nishiuchi, H. Yamamoto, and E. Wada, *Tetrahedron Lett.*, 1991, **32**, 6367; S. Kanemasa, M. Nishiuchi, and E. Wada, *Tetrahedron Lett.*, 1992, **33**, 1357; J. N. Kim, H. R. Kim, and E. K. Ryu, *Synth. Commun.*, 1993, **23**, 1673.
4. **3** (Entry 1): ^1H NMR (500 MHz, CDCl_3) δ 2.48 (d, 1H, $J = 6.2$ Hz), 2.80-3.10 (m, 4H), 3.55 (dd, 1H, $J = 4.8, 10.3$ Hz), 4.63-4.68 (m, 2H), 5.16 (s, 2H), 7.22-7.34 (m, 20H); MS m/z (relative intensity) 502 (M^+ , 9), 335 (8), 267 (35), 236 (27), 193 (7), 167 (100), 152 (21); HRMS calcd for $\text{C}_{33}\text{H}_{30}\text{N}_2\text{O}_3$ 502.2256, found 502.2258; IR (NaCl) ν_{max} 3436, 3058, 3027, 1598, 1494, 1452, 701 cm^{-1} . **3** (Entry 2): ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 3.36-3.53 (m, 4H), 3.63 (dd, 1H, $J = 5.4, 10.4$ Hz), 4.78-4.86 (m, 2H), 7.44-7.46 (m, 6H), 7.66-7.69 (m, 4H); MS m/z (relative intensity) 322 (M^+ , 1), 177 (38), 159 (15), 145 (84), 117 (100), 103 (61), 90 (38), 76 (92), 51 (22); HRMS calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$ 322.1317, found 322.1326; IR (NaCl) ν_{max} 3554, 3446, 3054, 3027, 2962, 1446, 1099, 912, 755, 690, 412 cm^{-1} . **3** (Entry 3): ^1H NMR (300 MHz, CDCl_3) δ 2.18 (s, 12H), 2.24 (s, 6H), 3.07-3.31 (m, 4H), 3.53-3.58 (m, 1H), 4.74-4.83 (m, 2H), 6.91 (s, 4H); MS m/z (relative intensity) 406 (M^+ , 30), 218 (17), 202 (10), 188 (100), 172 (6), 159 (82), 145 (30), 130 (18), 119 (31), 91 (21), 77 (9.87); HRMS calcd for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_3$ 406.2256, found 406.2250; IR (NaCl) ν_{max} 3318, 2971, 2931, 2912, 2854, 1652, 1427, 1384, 1118, 916 cm^{-1} . **3** (Entry 4): ^1H NMR (300 MHz, CDCl_3) δ 2.74 (d, 1H, $J = 5.5$ Hz), 3.40 (dd, 2H, $J = 8.9, 17.3$ Hz), 3.49 (dd, 2H, $J = 17.3, 10.4$ Hz), 3.99 (dd, 1H, $J = 5.5, 10.5$ Hz), 5.00-5.12 (m, 2H), 7.20-7.45 (m, 6H); MS m/z (relative intensity) 457 (M^+ , 12), 245 (45), 228 (27), 214 (100), 186 (66), 172 (25), 145 (21), 136 (13), 109 (14), 75 (12); HRMS calcd for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_3\text{Cl}_4$ 457.9758, found 457.9750. **3** (Entry 5): ^1H NMR (200 MHz, CDCl_3) δ 1.89 (s, 6H), 1.96 (s, 6H), 2.40 (d, 1H, $J = 6.6$ Hz), 3.21 (d, 4H, $J = 9.0$ Hz), 4.60-4.77 (m, 2H), 5.88 (s, 2H); MS m/z (relative intensity) 278 (M^+ , 9), 180 (25), 165 (21), 124 (52), 94 (28), 81 (46), 70 (32), 65 (29), 55 (100), 53 (28), 40 (90); HRMS calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3$ 278.1630, found 278.1630; IR (NaCl) ν_{max} 3318, 2971,

2931, 2856, 1652, 1384, 1118, 916 cm^{-1} .

5. **5**: ^1H NMR (500 MHz, CDCl_3) δ 1.92 (s, 6H), 1.95 (s, 3H), 2.81 (d, 4H, $J = 6.2$ Hz), 5.03 (s, 2H), 5.18 (t, 1H, $J = 5.2$ Hz), 5.39-5.45 (m, 2H), 7.14-7.35 (m, 20H); MS m/z (relative intensity) 634 (M^+ , 8), 467 (6), 425 (11), 407 (7), 365 (17), 347 (51), 305 (87), 287 (87), 165 (100), 105 (22); IR (NaCl) ν_{max} 2919, 2850, 2387, 1745, 1494, 1373, 1220, 1031, 701, 408 cm^{-1} .
6. **7** (Entry 1): ^1H NMR (500 MHz, CDCl_3) δ 2.72 (d, 2H, $J = 4.9$ Hz), 2.95 (dd, 2H, $J = 10.9, 17.1$ Hz), 3.05 (dd, 2H, $J = 7.6, 17.1$ Hz), 3.63-3.66 (m, 2H), 4.68-4.72 (m, 2H), 5.14 (s, 2H), 7.21-7.30 (m, 20H); MS m/z (relative intensity) 532 (M^+ , 11), 279 (7), 236 (46), 167 (100), 152 (19), 60 (5); HRMS calcd for $\text{C}_{34}\text{H}_{32}\text{N}_2\text{O}_4$ 532.2362, found 532.2362; IR (NaCl) ν_{max} 3428, 3060, 3027, 2927, 1598, 1494, 1452, 1256, 701 cm^{-1} . **7** (Entry 2): ^1H NMR (500 MHz, CDCl_3) δ 3.26-3.45 (m, 4H), 3.60-3.63 (m, 2H), 4.81-4.83 (m, 2H), 5.12-5.13 (m, 2H), 7.42-7.44 (m, 6H), 7.64-7.66 (m, 4H); MS m/z (relative intensity) 352 (M^+ , 7), 206 (10), 190 (10), 176 (13), 146 (100), 130 (8), 118 (34), 104 (37), 91 (13), 77 (41); HRMS calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4$ 352.1423, found 352.1419; IR (NaCl) ν_{max} 3507, 3405, 3303, 2917, 2389, 1446, 1357, 1081, 754, 688, 431 cm^{-1} . **7** (Entry 3): ^1H NMR (500 MHz, CDCl_3) δ 2.22-2.26 (m, 18H), 2.84 (d, 2H, $J = 5.4$ Hz), 3.25 (dd, 2H, $J = 10.9, 17.5$ Hz), 3.35 (dd, 2H, $J = 8.15, 17.5$ Hz), 3.89-3.91 (m, 2H), 4.91-4.96 (m, 2H), 6.87 (s, 4H); MS m/z (relative intensity) 436 (M^+ , 20), 249 (23), 218 (10), 188 (100), 158 (20), 146 (29), 119 (27), 91 (16), 77 (7); HRMS calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_4$ 436.2362, found 436.2371; IR (NaCl) ν_{max} 3421, 2921, 2856, 1612, 1434, 1328, 1093, 850 cm^{-1} .