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ETHYL N-DIENYL PYROGLUTAMATES: NOVEL ASYMMETRIC DIENES

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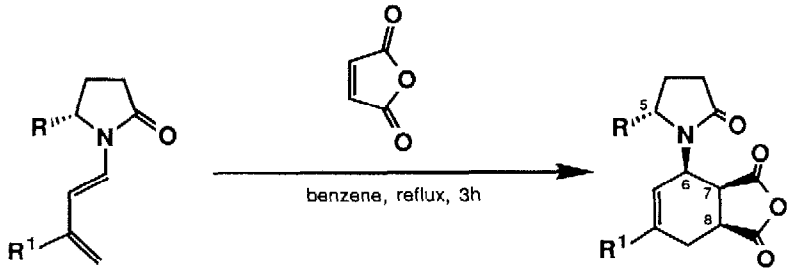
Abstract: Conversion of *L*-glutamic acid to *S*-ethyl pyroglutamate allows reaction with α,β-unsaturated aldehydes to give the N-dienyl derivative. The resulting dienyl pyroglutamates are new asymmetric dienes which show excellent diastereoselectivity in the Diels-Alder reaction with electron deficient alkenes.

The development of asymmetric Diels Alder reagents is increasingly important to synthesis. There are many reports of the preparation of asymmetric alkenes which are useful as dienophiles.[1,2] Oppolzer's work with camphenyl derivatives[2a,3] is illustrative and Houk has also described the characteristics of asymmetric acrylate derivatives.[4] There are fewer examples of asymmetric dienes which behave as enophiles in the Diels-Alder reaction,[2a] and they are usually generated for a specific synthetic purpose. Various asymmetric cyclopentadiene derivatives have been prepared by Vollhardt,[5] Paquette[6] and Winterfeldt.[7] Corey prepared an asymmetric butadienyl octahydronapthalene derivative.[8] Santelli prepared (1'-buten-3'-yl)-*p*-mentha-3,8-diene[9] and Kozikowski prepared a chiral 2-silyloxy-1,3-heptadiene derivative.[10] Carrie prepared an asymmetric dienyl alcohol from a dienyl iron complex.[11] A similar asymmetric diene was prepared by Roberts, via an enantioselective ester hydrolysis with a lipase isolated from *Mucor miehei*, to give the alcohol.[12] Oppolzer also utilized an asymmetric dienyl amide in a synthesis of pumiliotoxin-C.[13] Franck has described the Diels-Alder cyclization of several chiral allylic dienyl alcohols.[14] In addition, Franck described the various parameters which control diastereoface selectivity when the diene contains a stereogenic allylic center.[14]

The utility of dienyl amides and our interest in the chemistry of *N*-alkenyl lactams led us to examine the reactivity of lactams with α,β-unsaturated aldehydes. This reaction gave moderate to good yields of the corresponding *N*-dienyl lactam.[15] Only Murata and Terada, who prepared *N*-(1,3-butadienyl)-2-pyrrolidinone in 10% yield,[16] and Heck, who prepared *N*-(4-phenyl-1,3-butadienyl)-2-pyrrolidinone in 25% yield,[17] had previously generated dienyl lactams. These procedures were not convenient nor easily applicable to a variety of lactams and incorporation of substituents on the dienyl group was difficult. The *N*-dienyl amides were, in contrast, well-known. Overman had previously shown that *N*-dienyl amides were easily prepared[18] and showed good *endo* and *ortho* selectivity in the Diels-Alder reaction.[19] Similar results were reported by Oppolzer who developed synthetic routes to dienyl amides[20] and examined their intramolecular cyclization reactions.[13,21]

We have now shown that a new asymmetric dienyl lactam, ***1a***, can be easily prepared from *S*-ethyl pyroglutamate and an α,β-unsaturated aldehyde. This diene reacts with electron deficient alkenes to give excellent yields of the Diels-Alder adduct, with excellent diastereoselectivity. Other asymmetric dienes such as ***1*** can be prepared from a variety of α,β-unsaturated aldehydes. This report establishes their facile preparation and their diastereoselective, intermolecular Diels-Alder reactions with electron deficient alkenes. The stereogenic center is *not* allylic to the diene moiety but diastereoface selection is influenced by approach of the dienophile away from the C_5 carboethoxy group. Diastereoface selectivity is complicated, however, by the orientation of the diene moiety which may have the diene π-orbitals overlapped with the lactam π-orbitals (parallel) or perpendicular to the lactam π orbitals. Oppolzer suggested overlap of the π-orbitals was preferred.[13,21b] For ***1*** the *cisoid*-diene moiety required for the cyclization can be oriented with the diene carbons 'syn' or 'anti' to the carboethoxy group at C_5.



1 ***2***

(a) R = CO_2Et, R^1 = H (b) R = CO_2Et, R^1 = Me

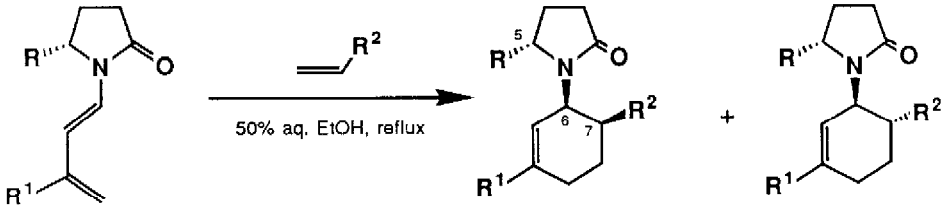
Silverman previously showed that *L*-glutamic acid was converted to *S*-ethyl pyroglutamate without loss of chirality.[22] Conversion of *S*-ethyl pyroglutamate to its *N*-dienyl derivative offered a facile route to a dienyl lactam which would be a new asymmetric diene. We had previously shown that dienyl lactams are excellent enophiles in the Diels-Alder reaction[15] showing *endo* and *ortho* selectivity similar to that reported by Overman and Oppolzer.

Reaction of *S*-ethyl pyroglutamate with acrolein (*p*-TsOH/$PhCH_3$/reflux) afforded a 39% yield of ***1a*** and reaction with 3-methylacrolein gave a 42% yield of ***1b***. In general, yields were reduced relative to similar reactions with 2-pyrrolidinone. Pyroglutamate is less reactive and volatile aldehyde co-reactants are lost during the condensation. The ready availability of all precursors, however, allowed synthetically useful amounts of ***1*** to be prepared without difficulty.

Reactions of ***1a*** and ***1b*** with maleic anhydride (benzene/reflux/3 h) gave a single diastereomeric product, ***2a*** and ***2b***, respectively, in 73% and 76% yield. Both are represented as the C_5 *S* C_6 *R* C_7 *S* C_8 *S* diastereomer. NMR studies revealed a *cis* relationship for C_6C_7 as well as for C_7C_8 . Spectroscopic analysis could not distinguish the *SRSS* and the *SSRR* diastereomers, however, and the oily nature of the products precluded x-ray analysis. The diacid hydrolysis product of ***2a*** was a solid, but crystallization gave a crystal whose morphology was incompatible with x-ray analysis. We also reacted ***1a*** with *N*–phenylmaleimide and observed a single diastereomeric product, as an oily semi-solid. Although the

adducts have defied attempts to obtain x-ray confirmation of their configuration,[23] formation of a single product clearly indicates excellent diastereoselectivity. None of the *trans* cycloadduct was detected by ^1H and ^{13}C NMR or by capillary GC/MS analysis. Satisfactory analyses were obtained for all compounds.

The ^1H NMR coupling constants for the dienyl protons are essentially the same as observed in the dienyl amides of Oppolzer[13,21b] and Overman.[18,19] If overlap of the diene π system with the lactam π orbitals is preferred, as suggested by Oppolzer, this may be the major orientation in ***1***. The *endo* transition state for approach of the dienophile is favored, analogous to the observations of Oppolzer,[21b] our previous work[15] and that of Overman and Houk.[19a] Models suggest that the 'parallel' diene orientation with the dienyl carbons 'syn' to C_5 (as shown in the drawing of ***1***) is less hindered when maleic anhydride is in close proximity. This orientation leads to a prediction of the C_5 *S* C_6 *R* C_7 *S* C_8 *S* diasteromer as the major cycloadduct when the dienophile approaches from the face opposite the *S*-carboethoxy group at C_5. This is, of course, speculative in the absence of x-ray data but is a reasonable possibility for the configuration of ***2a***.



1 ***3*** ***4***

(a) R = CO_2Et, R^1 = H, R^2 = CO_2Et
(b) R = CO_2Et, R^1 = Me, R^2 = CO_2Et
(c) R = CO_2Et, R^1 = H, R^2 = $\overset{O}{\overset{\|}{C}}$-$CH_3$

Reaction of ***1a*** with ethyl acrylate (50% aq. EtOH/reflux) gave a 91% yield of cycloadducts ***3a*** and ***4a***. ^1H and ^{13}C NMR studies indicated a 93:7 mixture of *cis* and *trans* adducts. This is essentially the same regioselectivity exhibited by 2-pyrrolidinone derivatives.[15] The diastereoselectivity was excellent giving a 91.5:1.0 and 6.5:0.1 mixture of products, for a 92:1 mixture of the *cis* diastereomers. ^1H NMR showed the coupling constant to be 6.2 Hz, supporting the *cis* C_6C_7 relationship. As with ***2***, ***5*** can be either C_5 *S* C_6 *R* C_7 *S* or C_5 *S* C_6 *S* C_7 *R*, but the selectivity for one diasteromer is clearly very good. The 65:1 ratio of diastereomeric *trans* adducts also indicates excellent diastereoselectivity. This ratio is based, however, on negligible amounts of the minor diasteromer observed by capillary GC/MS and is less accurate. Similar reaction with ***1b*** gave ***3b*** and ***4b*** in 77% yield as an 86.7:4.9 and 8.4:0.1 diastereomeric mixture. The 92:8 *cis-trans* ratio indicated similar regioselectivity as observed with ***1a*** but the diastereoselectivity was only 18:1 for the *cis* adduct of ***3b***. Although reasonable, the selectivity for the substituted diene was significantly less that the unsubstituted diene. The 84:1 ratio for ***4b*** is also based on negligible amounts of the minor isomer observed by capillary GC/MS.

We also examined the reactivity of ***1a*** with methyl vinyl ketone, which led to ***3c*** and ***4c*** in 79% yield as a 79.6:2.4 and 17.9:0.1 diastereomeric mixture of *cis* and *trans* isomers. The regioselectivity for the *cis* isomer was reduced to 82:18 but the diastereoselectivity was good, with the *cis* adduct showing a selectivity of 40:1. The 180:1 ratio for the *trans* adduct is again less accurate.

In conclusion, we have developed a new class of asymmetric dienyl lactams which are easy to prepare from the chiral precursor *L*-glutamic acid. The dienes show excellent reactivity in the Diels-Alder reaction with good to excellent diastereoselectivity. The preference for the *cis* (*endo*) adduct is similar to that observed with achiral dienyl lactams and dienyl amides. Further development of both inter- and intramolecular Diels-Alder reactions with these dienes or derivatives will have useful implications in alkaloid synthesis. These molecules are an interesting and useful addition to the growing list of asymmetric dienes exploited in the Diels-Alder reaction.

Literature Cited

1. Fallis, A.G. ***Can. J. Chem.***, (1984), ***52***, 183.
2. (a) Oppolzer, W. ***Angew. Chem. Int. Ed., Engl.***, (1984), ***24***, 876; (b) Oppolzer, W. ***Ibid.***, (1977), ***16***, 10; (c) Brieger, G.; Bennett, J.N. ***Chem. Rev.***, (1980), ***80***, 63; (d) Paquette, L.A. in "Asymmetric Synthesis", Vol. 3, Morrison, J.D. (Ed.), Academic Press, New York, (1984), pp. 455.
3. (a) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. ***Helv. Chim. Acta***, (1984), ***67***, 1397; (b) Oppolzer, W.; Dupuis, D. ***Tetrahedron Lett.***, (1985), ***26***, 5437; (c) Oppolzer, W.; Chapuis, C.; Kelly, M.J. ***Helv. Chim. Acta***, (1983), ***66***, 2358; (d) Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. ***Ibid.***, (1983), ***66***, 2100.
4. Loncharich, R.J.; Schwartz, T.R.; Houk, K.N. ***J. Amer. Chem. Soc.***, (1987), ***109***, 14.
5. Halterman, R.L.; Vollhardt, K.P.C. ***Tetrahedron Lett.***, (1986), ***27***, 1461 and reference 5 therein.
6. McLaughlin, M.L.; McKinney, J.A.; Paquette, L.A. ***Tetrahedron Lett.***, (1986), ***27***, 5595.
7. Schomburg, D.; Thielmann, M.; Winterfeldt, E. ***Tetrahedron Lett.***, (1986), ***27***, 5833; (1985), ***26***, 1705.
8. Corey, E.J.; Desai, M.C. ***Tetrahedron Lett.***, (1985), ***26***, 5747.
9. Pons, J.-M.; Santelli, M. ***Tetrahedron Lett.***, (1986), ***27***, 4153.
10. Kozikowski, A.P.; Nieduzak, T.R.; Springer, J.P. ***Tetrahedron Lett.***, (1986), ***27***, 819.
11. Gree, R.; Laabassi, M.; Mosset, P.; Carrie, L. ***Tetrahedron Lett.***, (1985), ***26***, 2317.
12. Roberts, S.M. ***Chem. & Industry***, (1988), 384.
13. Oppolzer, W.; Fröstl, W.; Weber, H.P. ***Helv. Chim. Acta***, (1975), ***58***, 593.
14. Tripathy, R.; Franck, R.W.; Onan, K.D. *J. Am. Chem. Soc.*, ***1988***, *110*, 3257
15. Zezza, C.A.; Smith, M.B. ***J. Org. Chem.***, (1988), ***53***, 1161.
16. Murata, K.; Terada, A. ***Bull. Chem. Soc. Jpn.***, (1967), ***43***, 414.
17. Ziegler Jr., C.B.; Heck, R.F. ***J. Org. Chem.***, (1978), ***43***, 2949.
18. (a) Overman, L.E.; Clizbe, L.A. ***J. Amer. Chem. Soc.***, (1976), ***88***, 2352, 8295; (b) Overman, L.E.; Taylor, G.F.; Jessup, P.J. ***Tetrahedron Lett.***, (1976), 3086; (c) Overman, L.E.; Taylor, G.F.; Petty, C.B.; Jessup, P. ***J. Org. Chem.***, (1978), ***43***, 2164; (d) Overman, L.E.; Clizbe, L.A.; Freerks, R.L.; Marlow, C.K. ***J. Amer. Chem. Soc.***, (1981), ***93***, 2807.
19. (a) Overman, L.E.; Taylor, G.F.; Houk, K.N.; Dommelsmith, L.N. ***J. Amer. Chem. Soc.***, (1978), ***90***, 3182; (b) Overman, L.E.; Jessup, P.J.; ***Ibid.***, (1978), ***90***, 5179; (c) Overman, L.E.; Freerks, R.L.; Petty, C.B.; Clizbe, L.A.; Ono, R.K.; Taylor, G.F.; Jessup, P.J. ***Ibid.***, (1971), ***83***, 3833.
20. Oppolzer, W.; Fröstl, W. ***Helv. Chim. Acta***, (1975), ***58***, 587.
21. (a) Oppolzer, W.; Bieber, L.; Francotte, E. ***Tetrahedron Lett***, (1979), 587; (b) Oppolzer, W.; Fröstl, W. ***Helv. Chim. Acta***, (1975), ***58***, 590; (c) Oppolzer, W. ***J. Amer. Chem. Soc.***, (1971), ***83***, 3833.
22. Silverman, R.B.; Levy, M.A. ***J. Org. Chem.***, (1980), ***45***, 815.
23. We also converted ***2a*** to the *cis*-diol via catalytic osmylation and obtained an oil. Diester ***3a*** was reduced with $LiAlH_4$ to the diol, an oily semi-solid. The diol was converted to the oily *bis*-3,5-dinitrobenzoate ester. We did not convert ***3c*** to a hydrazone derivative due to the tendency of the C_5 ester to racemize in acidic media. To date, all attempts to convert ***2*** or ***3*** to crystalline derivatives has failed.

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