CHEMISTRY LETTERS, pp. 1007-1008, 1983.

EFFICIENT SYNTHESIS OF ACETOXYFIMBROLIDES AND BECKERELIDES ANALOGS

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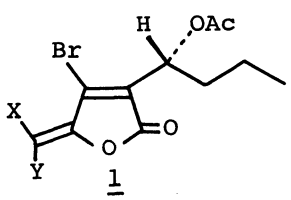
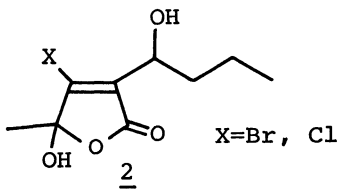
An efficient synthesis of acetoxyfimbrolides and beckerelides analogs has been developed *via* peracid oxidation of 2-methyl-4-(1-acetoxybutyl)furan as the key synthetic step. Antimicrobial activity of the products has also been tested.

Acetoxyfimbrolides 1 isolated from the red alga *Delisea fimbriata*[1] and related beckerelides 2 isolated from the red alga *Beckerella subcostatum*[2] have been



X	Y
Br	H
H	Br
I	H
H	I
H	Cl
Br	Br

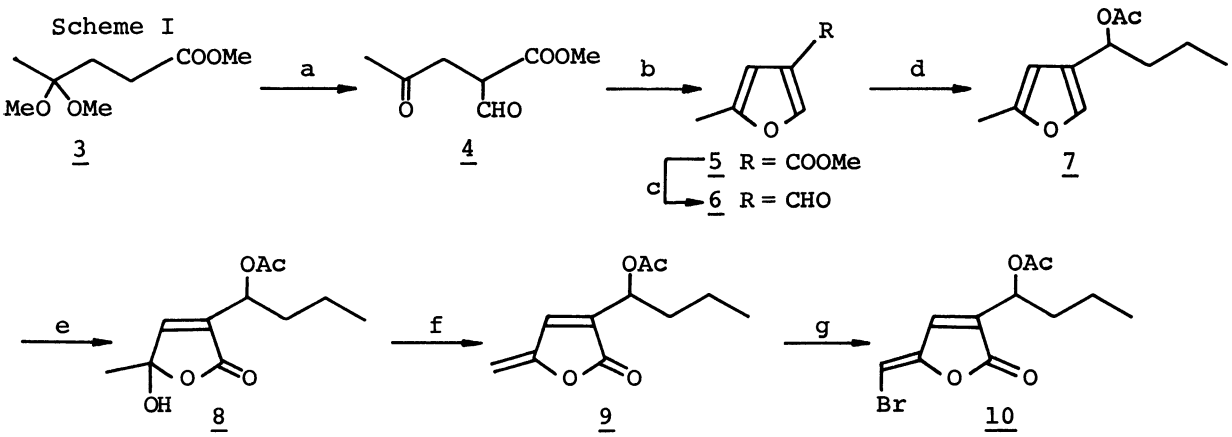


reported to exhibit antimicrobial activities. The interesting γ-methylenebutenolide skeleton of the former compounds has elicited considerable attention from synthetic chemists.[3] We report herein an efficient synthetic approach to acetoxyfimbrolides and beckerelides *via* oxidation of 2,4-disubstituted furan derivatives as the key synthetic step as outlined in Scheme I.

In order to realize our synthetic scheme, a new synthetic method of the requisite 2,4-disubstituted furan derivatives was developed as follows. Formylation of methyl levulinate dimethyl acetal 3 and subsequent hydrolysis afforded the very sensitive formyl ketone 4 in 88% crude yield. Treatment of 4 with Amberlyst H-15 in refluxing benzene resulted in smooth cyclization to methyl 5-methyl-3-furoate 5, bp 72°C/25 mmHg (lit[4] 80-83°C/29 mmHg), in 56% yield. Conversion of 5 to 3-formylfuran 6 followed by treatment with Grignard reagent and acetylation gave the desired furan derivative 7 in 43.3% overall yield.

Reaction of the furan 7 with 2 equiv of *m*-chloroperbenzoic acid in the presence of 2 equiv of $NaHCO_3$ in CH_2Cl_2 for 4.5 h at room temperature gave a diastereomeric mixture of hydroxybutenolides 8, beckerelides analogs, in 86% yield. The dehydration of 8 was accomplished by the treatment with phosphorus pentoxide[5] for 1.5 h in refluxing benzene to afford almost pure dehalogenated acetoxyfimbrolide (±)-9 in 70% yield; IR (Neat) 1780, 1740, 1650, 1620, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94(3H, t, J=7 Hz), 1.2-2.0(4H, m), 2.10(3H, s), 4.85(1H, d, J=2 Hz), 5.18(1H, d, J=2 Hz), 5.65(1H, t, J=7 Hz), 7.15(1H, s); *m/z* 211($M^+ + 1$). Bromination of 9 in

Scheme I



[a]LDA, THF, -30°C, then HCOOEt, then dil HCl. [b]Amberlyst H-15, C_6H_6, reflux, 2 h. [c]$LiAlH_4$, ether, then PDC, CH_2Cl_2. [d]*n*-PrMgI, ether, then Ac_2O-DMAP-Py. [e]MCPBA (95% assay, 2 equiv), $NaHCO_3$ (2 equiv), CH_2Cl_2, room temp, 4.5 h. [f]P_2O_5, C_6H_6, reflux, 1.5 h. [g]Br_2, hydroquinone (cat.), CH_2Cl_2, 0°C, then DBU, -10°C, 0.5 h.

CH_2Cl_2,[6] followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene gave a high yield (95%) of the monobrominated derivative (±)-10; ^{1}H NMR ($CDCl_3$) δ 0.91(3H, t, J=7 Hz), 1.2-1.9(4H, m), 2.07(3H, s), 5.60(1H, t, J=7 Hz), 6.03(1H, s), 7.13(1H, s).[7]

The debromoacetoxyfimbrolides 9 and 10 showed a strong antimicrobial activity against some fungi while 8 did not exhibit such an activity.[8]

This work was supported in part by a Grant-in-Aid for Scientific Research No. 56470026 from the Ministry of Education, Science and Culture.

References

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(Received April 18, 1983)